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BLZ945

Clinical Trial Protocol Title: CBLZ945C12201 / NCT04066244

# An open-label, adaptive design study in patients with amyotrophic lateral sclerosis (ALS) to characterize safety, tolerability and brain microglia response, as measured by TSPO binding, following multiple doses of BLZ945, using positron emission tomography (PET) with the radioligand [$^{11}$C]-PBR28

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## Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study procedures. Note: The SOM will not be a part of the Clinical Study Report.

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## List of abbreviations

| | |
|---|---|
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALS | Amyotrophic Lateral Sclerosis |
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| ALT | alanine aminotransferase |
| ANCA | anti-neutrophil cytoplasm antibodies |
| AST | aspartate aminotransferase |
| AxMP | Auxiliary Medicinal Product |
| BCRP | Breast Cancer Resistance Protein |
| BLRM | Bayesian Logistics Regression Model |
| BMI | Body Mass Index |
| BUN | blood urea nitrogen |
| C-SSRS | Columbia - Suicide Severity Rating Scale |
| CK | creatine kinase |
| CK-MB | creatine kinase myocardial band |
| CLR | Renal clearance |
| CNS | Central Nervous System |
| CRF | Case Report/Record Form (paper or electronic) |
| CRO | Contract Research Organization |
| CRP | C-reactive protein |
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| CSF-1R | Colony-stimulating factor 1 receptor |
| CSR | Clinical study report |
| CT | Computed Tomography |
| CTC | Common Toxicity Criteria |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTX-I | C-terminal telopeptide of type I collagen |
| CV | coefficient of variation |
| DDI | Drug drug interaction |
| DLT | Dose Limiting Toxicity |
| ECG | Electrocardiogram |
| ECM | Extracellular Matrix |
| EDC | Electronic Data Capture |
| ELISA | Enzyme-linked immunosorbent assay |
| eSource | Electronic Source |
| ESR | Erythrocyte Sedimentation Rate |
| EWOC | Escalation With Overdose Control |
| FSH | Follicle Stimulating Hormone |
| GCP | Good Clinical Practice |
| GFAP | Glial fibrillary acidic protein |

| | |
|---|---|
| GGT | Gamma-glutamyl transferase |
| GI | Gastrointestinal |
| GPMNB | Osteoactivin / transmembrane glycoprotein NMB |
| h | hour |
| HAB | High affinity binder |
| HIV | human immunodeficiency virus |
| HNV | home nursing visit |
| HRRT | High Resolution Research Tomography |
| i.v. | intravenous |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IgG | Immunoglobulin-G |
| IgM | Immunoglobulin-M |
| IL-1β | Interleukin 1β |
| IMP | Investigational Medicinal Product |
| irAE | Immune related adverse event |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| LAB | Low affinity binder |
| LDH | lactate dehydrogenase |
| LFT | Liver function test |
| LLOQ | lower limit of quantification |



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|---|---|
| LVEF | Left Ventricular Ejection Fraction |
| MAB | Mixed-affinity binder |
| MATE | Multi-drug and toxin extrusion transporter |
| MBq | megaBecquerel |
| MCV | Mean Corpuscular Volume |
| MedDRA | Medical dictionary for regulatory activities |
| mg | milligram(s) |
| mL | milliliter(s) |
| mrem | Milli roentgen equivalent man |
| MRI | Magnetic Resonance Imaging |
| mSv | millisievert |
| MTD | Maximum Tolerated Dose |
| NFL | Neurofilament Light |
| NSAIDs | Nonsteroidal Anti-inflammatory Drugs |
| NYHA | New York Heart Association |
| p75 ECD | Extracellular domain of p75 |

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|---|---|
| p.o. | oral |
| PBMC | Peripheral blood mononuclear cell |
| PBPK | Physiologically based pharmacokinetic |
| PCR | Polymerase Chain Reaction |
| PD | pharmacodynamic(s) |
| PET | Positron Emission Tomography |
| P-gp | P-glycoprotein |
| PINP | Procollagen type I N-propeptide |
| PK | pharmacokinetic(s) |

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|---|---|
| PT | prothrombin time |
| OAT | Organic Anion Transporter |
| OATP | Organic Anion Transporting Polypeptide |
| OCT | Organic Cation Transporter |
| QMS | Quality Management System |
| QTcF | QT interval corrected by Fridericia's formula |
| RA | Rheumatoid arthritis |

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|---|---|
| ROI | Region of interest |
| SAE | serious adverse event |
| sCR | serum creatinine |
| SD | standard deviation |
| SGOT | serum glutamic oxaloacetic transaminase |
| SGPT | serum glutamic pyruvic transaminase |
| SLE | Systemic lupus erythematosus |
| SOC | Standard of care |
| SOM | Site Operations Manual |
| sTREM2 | Soluble fragments of Triggering Receptor Expressed on Myeloid Cells 2 |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |
| SUVR | Standardized Uptake Value Ratio |

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|---|---|
| TD | Study Treatment Discontinuation |
| Trap-5b | Tartrate-resistant acid phosphatase 5b |
| TREM-2 | Triggering Receptor Expressed on Myeloid Cells 2 |
| TSPO | 18 kDa Translocator Protein |
| ULN | upper limit of normal |
| ULOQ | Upper Limit Of Quantification |
| UMNB scale | Upper Motor Neuron Burden scale |
| vs | versus |
| Vt | Volume of Distribution |
| WBC | white blood cell(s) |
| WoC | Withdrawal of Consent |

## Glossary of terms

| | |
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| Additional treatment | Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy) |
| Assessment | A procedure used to generate data required by the study |
| Auxiliary Medicinal Product (AxMP) | Medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., rescue medication, challenge agents, background treatment or medicinal products used to assess endpoints in the clinical trial). Concomitant therapy is not considered as AxMP. |
| Biologic Samples | A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant |
| Cohort | A specific group of participants fulfilling certain criteria |
| Control drug | A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug |
| Cycles | Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days) |
| Dosage | Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day) |
| Electronic Data Capture (EDC) | Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces.<br>EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care. |
| End of the Clinical Trial | The end of the clinical trial is defined as the last visit of the last participant. |
| Enrollment | Point/time of participant entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol). |
| eSource | eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate. |
| Healthy volunteer | A person with no known significant health problems who volunteers to be a study participant |
| Investigational drug/treatment | The drug whose properties are being tested in the study |
| Investigational Product/ Investigational Medicinal product | A pharmaceutical form of an active ingredient or placebo being tested or used as a reference (such as an active comparator) in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. |
| Medication pack number | A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system |
| Part | A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and |

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| | a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease. |
| Patient | An individual with the condition of interest. |
| Personal Data | Participant information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples. |
| Randomization number | A unique identifier assigned to each randomized participant, corresponding to a specific treatment arm assignment |
| Run in Failure | A participant who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to participant's medications or other intervention) |
| Screen Failure | A participant who is screened but is not treated or randomized |
| Source Data/Document | Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource |
| Study treatment | Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy |
| Study treatment discontinuation | When the participant permanently stops taking study treatment prior to the defined study treatment completion date |
| Subject | A trial participant (can be a healthy volunteer or a patient) |
| Subject number | A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc. |
| Treatment number | A unique identifier assigned in non-randomized studies to each dosed participant, corresponding to a specific treatment arm |
| Variable | A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study |
| Withdrawal of Consent (WoC) | Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data |

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## Protocol summary

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| **Protocol number** | BLZ945C12201 |
| **Full Title** | An open-label, adaptive design study in patients with amyotrophic lateral sclerosis (ALS) to characterize safety, tolerability and brain microglia response, as measured by TSPO binding, following multiple doses of BLZ945 using positron emission tomography (PET) with the radioligand [$^{11}$C]-PBR28 |
| **Brief title** | Study of safety and proof of the mechanism of BLZ945 in ALS patients |
| **Sponsor and Clinical Phase** | Novartis / Phase II |
| **Investigation type** | Oral Drug |
| **Study type** | Interventional |
| **Purpose and rationale** | The purpose of the study is to identify a dose (or doses) of BLZ945, that measurably decreases microglia in the brains of participants with amyotrophic lateral sclerosis (ALS), and to evaluate the safety and tolerability of BLZ945 in ALS participants at these doses and dosing regimens. Cohort 5 will evaluate the safety, microglia reduction (PET sub-study) CCI after repeated cycles of BLZ945 using two dose regimens over 12 weeks. PET imaging using [$^{11}$C]-PBR28, a PET ligand selective for the 18 kDa translocator protein (TSPO), is widely used as a biomarker of microglial numbers and activation. Following microglia reduction, the repopulation of microglia in ALS participants will be assessed.<br><br>In addition to the demonstration of proof of mechanism (PoM), the results of this Phase 2 study with PET imaging will be used for PK/PD modelling to guide dose selection for subsequent Phase 2 (PoC) and Phase 3 clinical studies.<br><br>The purpose of Cohort 5 is to evaluate two planned dosing regimens in order to inform future clinical studies in participants with ALS. The 24-week extended treatment aims to evaluate safety and tolerability of BLZ945 and maintenance of its pharmacodynamic effects with prolonged treatment. |
| **Primary Objective(s)** | • Cohorts 1-4 and Cohort 5 (PET Sub-study): To evaluate brain microglial reduction, as measured by reduction in TSPO binding, following treatment with BLZ945 in ALS participants by using PET imaging with [$^{11}$C]-PBR28.<br>• Cohort 5: To assess safety-related effects on ECM accumulation under BLZ945 treatment |
| **Secondary Objectives** | • Cohorts 1-5: To characterize the pharmacokinetics (PK) of BLZ945 in ALS participants<br>• Cohorts 1-5: To evaluate safety and tolerability of BLZ945 in ALS participants at the planned doses and dosing regimen(s)<br>• Cohorts 1-5: To assess the CYP2C8 pharmacogenomic-pharmacokinetic relationship |
| **Study design** | **Cohorts 1-4**<br><br>This is an exploratory, adaptive, open-label study of approximately 16 ALS participants in cohorts of 4 participants per cohort. Dosing at 300 mg, 600 mg and 1200 mg as well as two additional cohorts are planned at doses to be |

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| | determined, within the range of 150 to 1200 mg for the 4 days dosing regimen or at 300 mg for the 7 days dosing regimen. The follow-up period will continue until Day 19 (4 days dosing) or Day 22 (7 days dosing) with an End of Study visit on Day 36 (4 days dosing) or Day 40 (7 days dosing). The maximum study duration for each participant including the 42-day screening visit is 80 (4-day dosing) and 84 days (7-day dosing).<br><br>After each dosing cohort and prior to proceeding with dosing of the next cohort, a review of all available data will be conducted, including PD (% microglia reduction), and safety/tolerability (continuous review of adverse events, laboratory assessments, blood pressure and ECG data) data. PK data from the first three dosing cohorts (planned as 300 mg, 600 mg, 1200 mg) will be reviewed after the third dosing cohort prior to proceeding to the fourth dosing cohort. The PK review will be done to assist with the determination of the appropriate next dose(s). The PK data may be reviewed prior to the initiation of any dosing cohort should this information be determined by the Investigators and/or Sponsor as necessary for decision-making purposes. The decision to proceed to the next dose cohort will be made jointly between the Sponsor and the Investigator. If notable adverse events or safety concerns are found at one of the planned dose levels, the next planned dosing levels may be modified based on the available data from previous cohorts. The participants will be domiciled during the treatment period.<br><br>**Cohort 5**<br><br>Cohort 5 will include an open-label, randomized, 2 arm administration of repeated oral doses of BLZ945. Approximately 30 adult participants will be enrolled in this cohort. The cohort includes a screening period (up to 6 weeks), a 12-week open-label treatment period with two dosing regimens, followed by a 4-week safety follow-up in participants with a confirmed diagnosis of ALS. Participants will be randomized in a 1:1 ratio across two dosing regimens: 600 mg BLZ945 the first 4 days of a two-week period in repeated cycles i.e. 4 days on and 10 days off (4/10) or 400 mg BLZ945 once a week (QW). A PET sub-study will enroll approximately 4 participants in each arm at specific study sites. Commercially Confidential Information Participants may have the option for selected study visits to occur on an outpatient basis in conjunction with home nursing on four visit days during the treatment period.<br><br>After the completion of the Follow up period (Week 16 visit), eligible participants will be offered to continue treatment with BLZ945 for an additional 24 weeks. |
| **Population** | The study population will be comprised of adults at least 18 years of age with clinically probable laboratory supported, or definite ALS according to the World Federation of Neurology Revised El Escorial criteria (Ludolph et al 2015). |
| **Key Inclusion criteria** | 1. Able to communicate well with the investigator, to understand and comply with the visits and procedures of the study.<br>2. Written informed consent must be obtained before any assessment is performed.<br>3. Male and female participants of at least 18 years of age, who are diagnosed with familial or sporadic ALS according to the World Federation of Neurology Revised El Escorial criteria of either bulbar or limb onset.<br>4a. Cohort 1-4: Able to swallow medication capsules, in the opinion of the investigator.<br>5. Disease duration from symptoms onset no longer than 48 months at the screening visit. |

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| | 6. Participants undergoing PET assessments: Having a SVC (slow vital capacity) equal to or more than 60% predicted normal value per local standards for gender, height, and age at the screening visit.<br>7a. Females of childbearing potential must have a negative pregnancy test at screening and/or baseline.<br>8a. Participants undergoing PET assessments: High-affinity binders (HAB) to TSPO, as evaluated by genotyping for the rs6971 polymorphism in the TSPO gene at the screening visit.<br>9. Participants undergoing PET assessments: Baseline PET scan of sufficient image quality, as determined by the PET experts, for the measurement of [$^{11}$C]-PBR28 volume of distribution (Vt) in the relevant CNS regions.<br>10b. Treatment with currently approved therapies is allowed, but participants need to be on a stable dose and regimen for at least 30 days prior to baseline. In case of riluzole, participants need to be on a stable dose and regimen for at least 90 days prior to baseline. In case for edaravone, the participant can be included if the initial BLZ945 dosing days can be scheduled off period of the edaravone treatment regimen.<br>11. Participants undergoing PET assessments: An Upper Motor Neuron Burden (UMNB) scale level ≥25 at the screening visit.<br>12. Participants undergoing PET assessments: BMI between 18 – 35 kg/m$^2$ at the screening visit.<br>13. Cohort 5 extended treatment period: Written informed consent for the extended treatment must be obtained before any assessment in the extended treatment period is performed.<br>14. Cohort 5 extended treatment period: Having completed the 12-week treatment period and the 4-week follow-up.<br>15. Cohort 5 extended treatment period: Females of childbearing potential must have a negative pregnancy test at Week 16 and agree to continue the contraception methods used in the treatment period. |
| **Key Exclusion criteria** | 1a. A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities at screening and/or baseline<br>• QTcF > 450 msec (males)<br>• QTcF > 460 msec (females)<br>2. Active hematologic, hepatic, or respiratory disorders that are clinically significant and may jeopardize the participant's safety if participating in the study or limit his/her participation in the study, including ability to tolerate the imaging studies.<br>3. Active dementia, neurologic diseases other than ALS, or psychiatric illness, that in the opinion of the investigator would limit their participation in the current study.<br>4. Use of other investigational drugs within 5 half-lives of screening, or until the expected PD effect has returned to baseline, whichever is longer; or longer if required by local regulations.<br>5. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes.<br>6. Presence of human immunodeficiency virus (HIV) infection based on screening lab results.<br>7. Evidence of active or latent tuberculosis as assessed by Quantiferon or similar testing as per local practice at screening.<br>8. Positive serology for hepatitis B surface antigen, or hepatitis C antibodies confirmed by an appropriate licensed test at screening. |

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| | 9a. Signs or symptoms, in the judgement of the investigator, of a clinically significant systemic viral, bacterial or fungal infection within 30 days prior to the screening visit.<br>COVID-19 specifically: COVID-19 testing as per local practice will be completed within 3 days prior to first dosing. Positive COVID-19 results would exclude participants from being enrolled into this study.<br>10a. Cardiac disorders, such as recent cardiac history (within 6 months) of acute coronary syndrome, acute heart failure, or significant ventricular arrhythmia at the screening visit or participants with a history of severe pulmonary hypertension, or cardiac failure class 3 or 4 of the NYHA classification, or history of reduced LVEF (<45%), or individuals with implanted cardiac pacemaker, or defibrillator.<br>11. Any of the following abnormal laboratory values at the screening visit:<br>• Total white blood cell count (WBC) outside the range of 1,500-15,000/$mm^3$ (1.5-15.0 x $10^9$/L)<br>• Platelets< 100,000/$mm^3$ (100 x $10^9$/L)<br>• Hemoglobin (Hgb) < 8.0 g/dL (<0.5 mmol / L)<br>• Lymphocyte count <500/$mm^3$ (<0.5 X $10^9$ / L)<br>12. Clinical evidence of liver disease or liver injury or any of the following hepatic conditions at the screening visit:<br>• Active chronic liver or biliary disease<br>• Direct bilirubin greater than the 1.5 x ULN<br>• Alkaline phosphatase (AP) greater than 3 x ULN<br>• AST (SGOT), ALT (SGPT) greater than 3 x ULN<br>• Gamma-glutamyl-transferase (GGT) > than 3 x ULN<br>13. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 14 days after last dose of BLZ945. Highly effective contraception methods include:<br>• Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.<br>• Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.<br>• Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.<br>• Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example, hormone vaginal ring or transdermal hormone contraception<br>In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.<br>14. Pregnant or nursing female participants.<br>15. Sexually active males unless they use a condom during intercourse while |

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| | taking the drug during treatment, for 14 days after stopping BLZ945 and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via semen.<br>16. Intentionally left blank; removed in amendment 02<br>17. Participants undergoing PET assessments: Any contraindications to MRI, including but not limited to the following:<br>• Brain Aneurysm Clip<br>• Implanted cardiac pacemaker, pacemaker wires or defibrillator<br>• Prosthetic heart valves<br>• Cochlear implant<br>• Ocular foreign body (e.g. metal shavings)<br>• Implanted insulin pump<br>• Tattoos (as determined by radiologist)<br>• Known claustrophobia<br>18. Taking medications prohibited by the protocol (see Section 6.2.2 (Prohibited medication) or Table 6-4 (Prohibited medication/procedure)).<br>19a. Participants undergoing PET assessments: Any contraindications to the line sampling, including but not limited to the following:<br>• Thromboangiitis obliterans (Buerger disease)<br>• Full-thickness burns over the cannulation site<br>• Inadequate circulation to the extremity<br>• Raynaud syndrome<br>• Coagulopathy<br>• Inadequate collateral flow<br>• Infection at the cannulation site<br>• Partial-thickness burn at the cannulation site<br>• Previous surgery in the area<br>• Synthetic vascular graft in the area<br>20. History or presence of impaired renal function as indicated by clinically significantly abnormal creatinine or BUN and/or urea values, or abnormal urinary constituents (e.g., albuminuria) at the screening visit.<br>21. Active suicidal ideation as measured by a response of “yes” on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS, if this ideation occurred in the past 6 months; or “yes” on any item of the Suicidal Behavior section, except for the “Non-Suicidal Self-Injurious Behavior” question of that section of the C-SSRS, if this behavior occurred in the past 2 years. A response of "Yes" to these questions is considered exclusionary at screening.<br>22a. History of drug abuse or harmful alcohol use within the 12 months prior to dosing within the judgement of the investigator and the below definition, or evidence of such abuse as indicated by the laboratory assays conducted during screening. Harmful alcohol use is defined as a history of, or current alcohol misuse/abuse, defined as “Five or more standard drinks on the same occasion on each of 5 or more days in the past 30 days prior to screening."<br>23. Inability or unwillingness to undergo repeated venipuncture or arterial cannulation, or in the opinion of the investigator, participant would be at an increased risk for adverse events related to these procedures.<br><br>Additional criteria applicable to Cohort 5 only: |

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| | 24. Active GI conditions such as Barrett's esophagus, achalasia, esophageal varices and active or history of esophageal cancer, pre-existing pancreatic disease<br>25. History of active vasculitis or history of autoimmune disease associated with vasculitis (eg. RA, SLE, Sjögrens disease, scleroderma)<br>26. History or current cardiac valve disorder, such as clinically significant stenosis or regurgitation (CTCAE grade ≥2), congenital valve disease, or other clinical condition that might affect cardiac valve function (excluding hemodynamically insignificant mitral valve prolapse)<br>27. Use of systemic anticoagulation that cannot be temporarily paused before study procedures (LP arterial line placement for PET scan)<br>28. Cohort 5 extended treatment period: Participants who are planning to initiate treatment with an additional approved ALS therapy in the next 24 weeks<br>29a. Cohort 5 extended treatment period: Clinically relevant changes on CT scan or echocardiography, signs of vasculitis, or evidence of a significant medical condition meeting treatment discontinuation criteria at EoT1 or EoS1 visits even if finding has resolved at EoS1 |
| **Study treatment** | BLZ945 (sotuletinib) |
| **Efficacy assessments** | • Cohorts 1-5: PET imaging of [$^{11}$C]-PBR28 binding as a measure of the pharmacodynamic effect of BLZ945 on brain microglia. |
| **Key safety assessments** | • Cohorts 1-5: Adverse event monitoring, Physical examinations, monitoring of laboratory markers in blood and urine, ECG.<br>• Cohort 5: Echocardiogram, CT scan |
| **Other assessments** | Commercially Confidential Information |
| **Data analysis** | Analysis of the primary objective:<br>1. Cohorts 1-4: Change of Vt in different brain regions as assessed by [$^{11}$C]-PBR28 PET imaging, from baseline after BLZ945 treatment<br>2. Cohort 5: The percent change from baseline to Week 12 in Vt measured via PET scan.<br>3. Cohort 5: The changes from baseline to Week 12 in: esophagus wall |

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| | thickness (mm) and LVEF (%)<br>4. Cohort 5: Any worsening from baseline to Week 12 in cardiac valve thickness and cardiac valve function (stenosis and regurgitation).<br>5. Cohort 5: Adverse events of ECM accumulation during the first 12 weeks of treatment.<br><br>Analysis of the secondary objective:<br>1. Cohorts 1-5: Frequency of relevant findings on physical examination, neurological examination, vital signs, hematology, chemistry, urinalysis, ECG evaluation, AE and SAE recordings<br>2. Cohorts 1-4: Relative change from baseline in % in Vt of [$^{11}$C]-PBR-28 after BLZ945 treatment depending on the pharmacokinetic exposure of BLZ945 PK assessment<br>3. Cohorts 1-4: Relative change from baseline in % in Vt of [$^{11}$C]-PBR28 after BLZ945 treatment versus other PD markers<br>4. Cohorts 1-4: Relative change from baseline in % in Vt [$^{11}$C]-PBR28, at 4 or 10 or 15 days post treatment cessation<br>5. Commercially Confidential Information<br>6. Cohort 5: BLZ945 plasma PK parameters on Day 4 (Arm #1) or on Day 1 (Arm #2) |
| **Key words** | Phase II, BLZ945, CSF-1R, Safety, [11C]-PBR28 |

# 1 Introduction

## 1.1 Background

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease caused by progressive loss of motoneurons (MNs) in the motor cortex, brainstem and spinal cord. It manifests with skeletal muscle weakness, spasticity and progressive paralysis, leading to the death of subjects by respiratory failure 3 to 5 years after diagnosis (Kiernan et al 2011). Although some drugs are currently approved for the treatment of ALS, none offer a significant improvement in survival of individuals with ALS. Thus, there is a significant unmet medical need for the treatment of ALS. Neuroinflammation plays a key role in many neurodegenerative diseases including ALS (Rodríguez, Mahy 2016). Indeed, an important pathophysiological mechanism in ALS is microglial activation, that is associated with degenerative motor neurons. Further, recent evidence links macrophage colony-stimulating factor 1 receptor (CSF-1R)-dependent microgliosis with ALS disease progression (Martínez-Muriana et al 2016).

Upon activation, microglial cells demonstrate increased expression of the 18 kDa translocator protein (TSPO). [$^{11}$C]-PBR28 is a positron emission tomography (PET) radiotracer for TSPO that is used to image neuroinflammation *in vivo* (Albrecht et al 2018, Zürcher et al 2015, Alshikho et al 2016, Alshikho et al 2018). Further references in the protocol to measures of change in microglia refer to TSPO binding, which is a measure of microglial content.

BLZ945 (sotuletinib) is a potent and selective low molecular weight tyrosine kinase inhibitor of the receptor CSF-1R. It shows functional activity in *in vitro* assays with normal human donor peripheral blood mononuclear cells as well as in transgenic mouse models. In animal models of ALS (SOD1G93A mice) BLZ945 showed dose-dependent microglia clearance as well as dose-dependent beneficial effects on weight maintenance and reductions in decline of grip strength. For additional information on BLZ945, please refer to the Investigator Brochure. Novartis is developing BLZ945 as a potential disease-modifying oral treatment for ALS by targeting microglia cells.

The planned study will evaluate the effect of BLZ945 on neuroinflammation in participants with ALS as measured by [$^{11}$C]-PBR28 PET imaging. Preliminary results from Cohorts 1-4, suggest that microglia reduction following BLZ945 dosing may persist for up to 10 days off drug, suggesting that there could be a cumulative effect with repeated dosing cycles. The planned Cohort 5 will evaluate the safety and tolerability of BLZ945 with the administration of repeated dosing cycles, as well as evaluate the effect on neuroinflammation as measured by [$^{11}$C]-PBR28 PET imaging (PET Sub-study) CCI

Data on microglia reduction and safety will be assessed to demonstrate proof of mechanism and to select potential doses of BLZ945 for future studies in ALS participants. Expected adverse events include elevation of transaminases (AST/ALT) and creatine kinase (CK) due to reduction in hepatic Kupffer cells, which share a macrophage lineage with microglia and are responsible for liver transaminase and CK clearance. CCI

Commercially Confidential Information Periorbital, orbital, eyelid, and face swelling has been observed in a study of BLZ945 in patients with advanced solid tumors (CBLZ945X2101) after treatment with BLZ945 and have been reported in studies with other CSF-1 and CSF-1R inhibitors (Pognan et al 2019). CCI

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## 1.2 Purpose

The purpose of Cohorts 1-4 of this study is to identify a dose (or doses) of BLZ945, that decrease(s) TSPO binding by at least 20% in the brain of ALS participants, and to evaluate the safety and tolerability of BLZ945 in ALS participants at these doses and dosing regimen.

PET imaging with a ligand selective for TSPO is widely used as a marker for microglial activation. Following microglia reduction, the repopulation of microglia in ALS participants will be assessed at different times post dosing.

Since there is no established clinically meaningful threshold for reduction of activated microglia, a threshold of a decrease of 20% has been chosen since this exceeds the published variability of the [$^{11}$C]-PBR28 PET imaging biomarker (5-10%) and would therefore be of sufficient magnitude to be unlikely to be the result of chance.

The purpose of Cohort 5 is to evaluate the safety, microglia reduction (PET sub-study) and the changes in blood Commercially Confidential Information after repeated cycles of BLZ945 using two dosing regimens over 12 weeks. The 24-week extended treatment to Cohort 5 aims to evaluate safety and tolerability of BLZ945 and maintenance of its pharmacodynamic effects with prolonged treatment.

# 2 Objectives and endpoints

**Table 2-1 Objectives and related endpoints**

| Objective(s) | Endpoint(s) |
|---|---|
| **Primary objective(s)** | **Endpoint(s) for primary objective(s)** |
| • Cohorts 1-4 and Cohort 5 (PET Sub-study): To evaluate brain microglial reduction, as measured by reduction in TSPO binding, following treatment with BLZ945 in ALS participants by using PET imaging with [$^{11}$C]-PBR28 | • Volume of distribution (Vt) in different brain regions for each [$^{11}$C]-PBR28 PET scan, and change after BLZ945 treatment<br>• Cohorts 1-4: at Day 5 (or 8) following 4 (or 7) oral doses of BLZ945 compared to baseline<br>• Cohort 5 (PET sub-study): at Week 12 following repeated cycles of BLZ945 compared to baseline |
| • Cohort 5: To assess safety-related effects on ECM accumulation under BLZ945 treatment | • Cohort 5: Changes in esophageal wall thickness (based on CT-scans) at Week 12 compared to baseline |

| Objective(s) | Endpoint(s) |
|---|---|
| | • Cohort 5: Cardiac valve thickness, cardiac valve function (stenosis and regurgitation based on echocardiography) and Left Ventricular Ejection Fraction (LVEF) as indicator of cardiac function (based on echocardiography) at Week 12compared to baseline<br>• Incidence of AEs related to ECM accumulation during the first 12 weeks of treatment |
| **Secondary objective(s)** | **Endpoint(s) for secondary objective(s)** |
| • Cohorts 1-5: To characterize the pharmacokinetics (PK) of BLZ945 in participants with ALS. | • Cohort 1-4:<br>  • Plasma: PK parameters on Day 1 and Day of last treatment (Day 4 or Day 7) (e.g. Cmax, Tmax, AUC, T1/2).Urine: renal clearance (CLR) on Day 1 and Day of last treatment (Day 4 or Day 7)<br>• Cohort 5: BLZ945 plasma concentrations and selected PK parameters (Cmax, Tmax, AUClast, Tlast) on Day 1 (Arm #2) and Day 4 (Arm #1) as feasible |
| • Cohorts 1-5: To evaluate safety and tolerability of BLZ945 in participants with ALS at the planned doses and dosing regimen. | • Cohorts 1-5: Relevant clinical findings - as per assessment schedule - on physical examination, neurological examination, vital signs, hematology, chemistry, urinalysis, ECG evaluation, AE and SAE recordings during the entire duration of the study (including extended treatment period) |
| • Cohorts 1-5: To assess the CYP2C8 pharmacogenomic-pharmacokinetic relationship | • CYP2C8 genotypes and BLZ945 plasma PK parameters |

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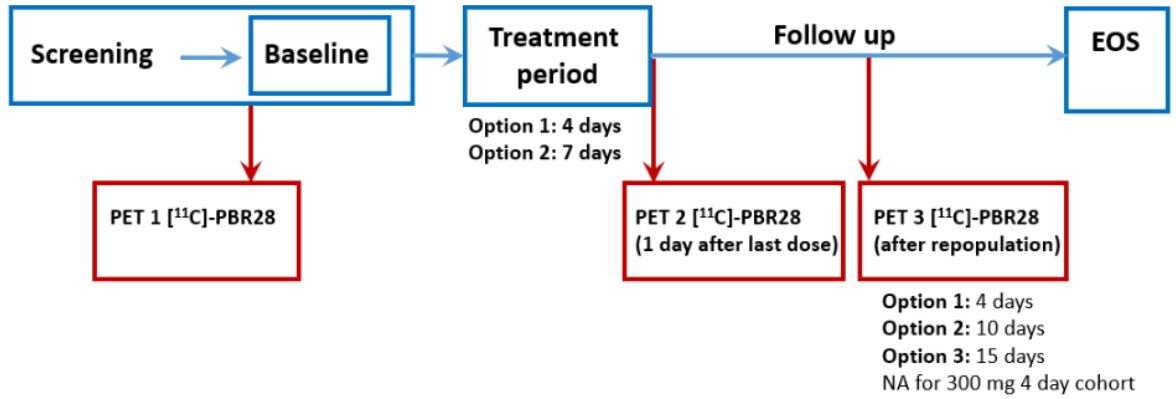
# 3 Study design

## 3.1 Cohorts 1-4

This study is an exploratory, adaptive, open-label study of a single treatment cycle of multiple oral doses of BLZ945 in ALS participants, administered using either a 4 days on / 10 days off or a 7 days on 7 days off treatment regimen.

The first four cohorts in the study consist of an up to 42-day screening and baseline period, a treatment period of a minimum of 4 days and a maximum of 7 days, a follow-up period until day 36 (for 4 day cohorts) or day 40 (for 7 day cohorts) (during this period repopulation of microglia will be assessed); see Figure 3-1. The maximum study duration for each participant, including the 42-day screening visit, is 80 days for the 4-day cohorts and 84 days for the 7-day cohort.

**Figure 3-1 Study design Cohorts 1-4**




This is a multiple ascending dose study with the starting dose of 300 mg daily for four days. After each dosing cohort and before proceeding to the next cohort, a review of all available data will be conducted, including pharmacodynamic (PD) (% microglial reduction), and safety/tolerability (continued review of adverse events, laboratory assessments, blood pressure and ECG data) data. PK data from the first three dosing cohorts (planned as 300 mg, 600 mg, 1200 mg) will be reviewed after the third dosing cohort prior to proceeding to the fourth dosing cohort. The PK review will be done to assist with the determination of the appropriate next dose(s). The PK data may be reviewed prior to the initiation of any dosing cohort should this information be determined by the Investigators and/or Sponsor as necessary for decision-making purposes. The decision to proceed to the next dose cohort will be made jointly between the Sponsor and the Investigator.

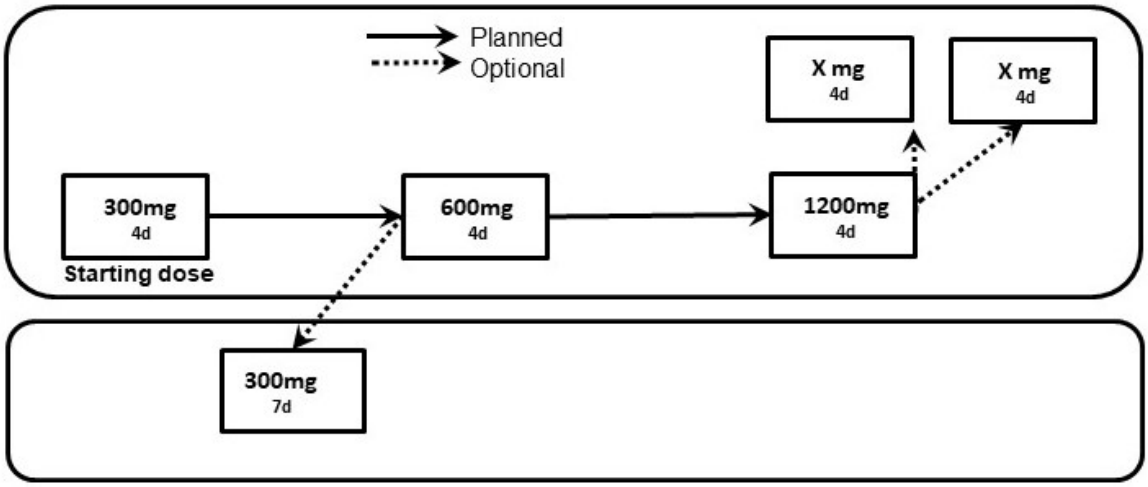
Dosing will continue according to the dose escalation schedule shown in Figure 3-2. If a decision is made not to proceed to the next (higher) planned dose, according to the dose escalation criteria outlined in Section 6.5.1 then dosing may be resumed at 300 mg and the dosing regimen may be extended to 7 days of BLZ945, as indicated in Figure 3-2. Alternatively, following a review of the available data and discussion between the Sponsor and the Investigator, if notable adverse events or safety concerns are found at one of the planned dose levels, the next planned 4-day dosing level may be modified (within the range of 150 mg to 1200 mg) based on the available data from previous cohorts.

The first dosing cohort will receive a dose of 300 mg per day. A total of five cohorts are planned (300 mg, 600 mg, 1200 mg, plus two additional cohorts at doses to be determined between 150 mg and 1200 mg, inclusive). The dose for the two additional cohorts will be determined by a decision algorithm. The recommended dose and dose regimen for the next cohort of participants (as per Figure 3-2) will be guided by the BLRM (Bayesian Logistic Regression Model) with EWOC (Escalation with overdose control) principle. The general

approach will be to fit an Emax model to TSPO binding as a measure of microglial reduction data at Day 5. An informative prior distribution for the parameters will be derived from available animal data (See Table 4-1). Prior distributions will be determined before study start, and documented in the Statistical Analysis Plan. After each cohort of 4 participants, the posterior distributions of the efficacy curve will be updated, and the next dose and number of doses chosen. Clinical judgement will always be used in combination with the recommendation of the dose-finding algorithm when the next cohort is to be dosed. Dose and dose duration modification decisions will be made by Investigators and Novartis study personnel. Decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study including safety information, DLTs, all CTCAE Grade ≥ 2 toxicity data, PK, and PD data from evaluable participants.

For further details on the decision to dose escalate, see Section 6.5.

**Figure 3-2 The different cohorts in the adaptive design (Cohorts 1-4)**




Note: a 800 mg dose was selected for Cohort 4

Each participant will undergo:

- The screening and baseline visit to assess eligibility.
- An MRI at the end of screening period (after rs6971 genotype is known, and eligibility is confirmed from the other screening visit assessments) for delineation of the brain regions of interest (ROIs), through either stand-alone MRI or during PET/MRI scanning if PET/MRI is used. Safety assessments during screening/baseline, treatment and EOS periods will be performed according to the assessment schedule and PK samples will be collected prior to dosing and at the time points after dosing as indicated in the assessment schedule (Table 8-1, Table 8-2, Table 8-3, Table 8-4).
- A maximum of three PET scans are scheduled (maximum total effective radiation dose of approx. 6.93 mSv per participant). These will include the baseline PET scan and up to two additional PET scans, which will be performed following the multiple dose administration of BLZ945. The 2nd PET scan will be performed one day after last dosing, and the 3rd PET scan as per Figure 3-3. Refer to Table 8-1 and Table 8-3 for accepted visit windows.

A transmission scan for attenuation correction will be acquired before each PET scan using an appropriate method [example: a $^{137}$Cs point source or a low dose CT scan depending on the PET system used, i.e. High Resolution Research Tomography (HRRT) or PET/CT (maximum total effective radiation dose of approx. 8.1 mSv per participant if CT is used for attenuation correction)].

- 1st PET Scan
  - In order for the participant to be eligible for the study and be dosed with BLZ945, the baseline PET scan (which is taken during screening period and at latest at baseline) must be of sufficient image quality to enable the measurement of Vt in the relevant brain regions.
- 2nd and 3rd PET Scan
  - The 4 participants in the first cohort (300 mg) will have a 2nd PET scan with [$^{11}$C]-PBR28 one day after the last BLZ945 administration (Day 5) to assess microglial reduction.
  - The repopulation of microglia will be assessed during the 3rd PET scan. Because the TSPO binding is anticipated to only minimally decrease at the 300 mg dose, no 3rd PET scan will be acquired in the first cohort. For subsequent cohorts, a 3rd PET scan will be acquired to evaluate repopulation of microglia. The 3rd PET scan will be performed 10 days after last dose (Day 14 or Day 17) in the second cohort. The timing of the 3rd PET scan for the next cohort(s) will be determined after review of the results of the previous cohort(s).

    If the TSPO binding signal in the motor cortex in the 3rd PET scan has already returned to at least 80% of the baseline level by 10 days after treatment cessation, then the 3rd PET scan may be performed earlier (relative to treatment cessation) for the next cohort(s).

    If the TSPO binding signal in the motor cortex has not returned to 80% of the baseline signal by 10 days after treatment cessation, then the 3rd PET scan may be performed later (relative to treatment cessation) in the next cohort(s) (See Figure 3-3).

    The decision regarding the timing of the 3rd PET scan will be made jointly between the Sponsor and the Investigator during the dose escalation decision meeting.

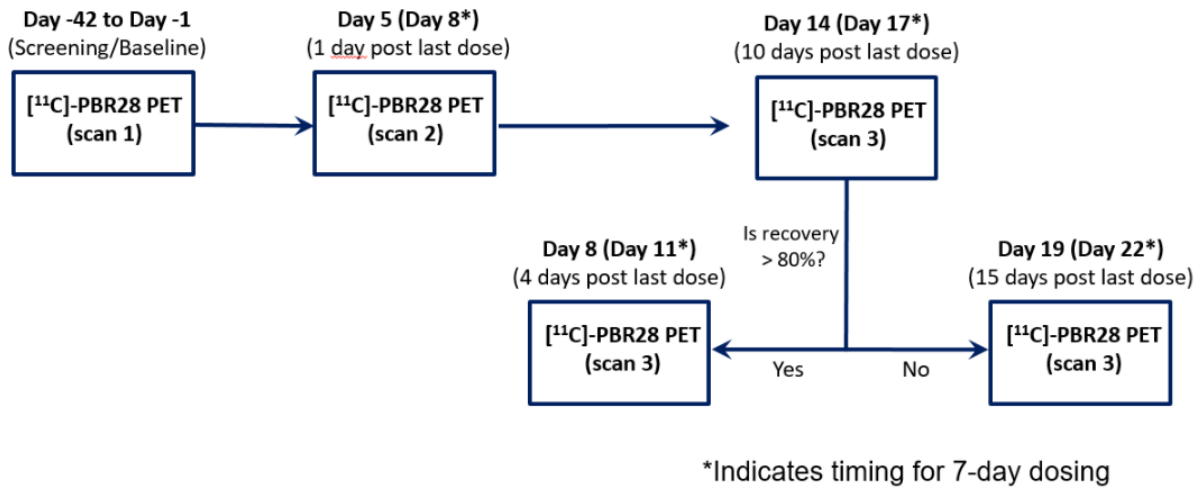
    If the data suggest that the pre-defined time points for the 2nd and 3rd PET scans are not properly timed to capture either the maximal effect on microglial reduction or repopulation, then the 2nd and 3rd PET scan time points may be further revised, as described in the SOM.

    If the 2nd or 3rd PET scan cannot be performed on the planned day for any reason, the assessment can be scheduled per the visit windows stated in the assessment schedule.

- Participants in the subsequent cohorts (Cohorts 2 to 4) will undergo identical assessments with the exception of the BLZ945 dose (and possibly dosing duration) and the timing of the post-dose PET scans.

For Cohorts 1-3, the 3rd PET scan was conducted on Day 14. Following a review of the data from Cohorts 1-3, which showed that the TSPO PET signal had not returned to at least 80% of the baseline, the 3rd PET scan in Cohort 4 was performed at Day 19.

**Figure 3-3 Decision algorithm for the timing of the third PET scan in subsequent cohorts up to Cohort 4 (for dosing cohorts above 300 mg / day)**

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At the time of amendment 5, Cohorts 1-4 have been completed. In each cohort, 4 participants received 300 mg (Cohort 1), 600 mg (Cohort 2), 1200 mg (Cohort 3) or 800 mg (Cohort 4) BLZ945 over 4 days. Following review of the data from the first three cohorts, supported by PK modeling, 800 mg over 4 days of dosing was selected as the dose level for Cohort 4. The planned 7 days dosing cohort was not conducted and will not be considered further.

## 3.2 Cohort 5

Cohort 5 will consist of an open-label, randomized, two-arms study investigating two BLZ945 dosing regimens. Participants with confirmed diagnosis of ALS will receive repeated treatment cycles of BLZ945 either 4 days on followed by 10 days off or once weekly.

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Approximately, a total of 40 participants are planned to be enrolled in Cohort 5 (also see replacement policy Section 9.1.1.2).

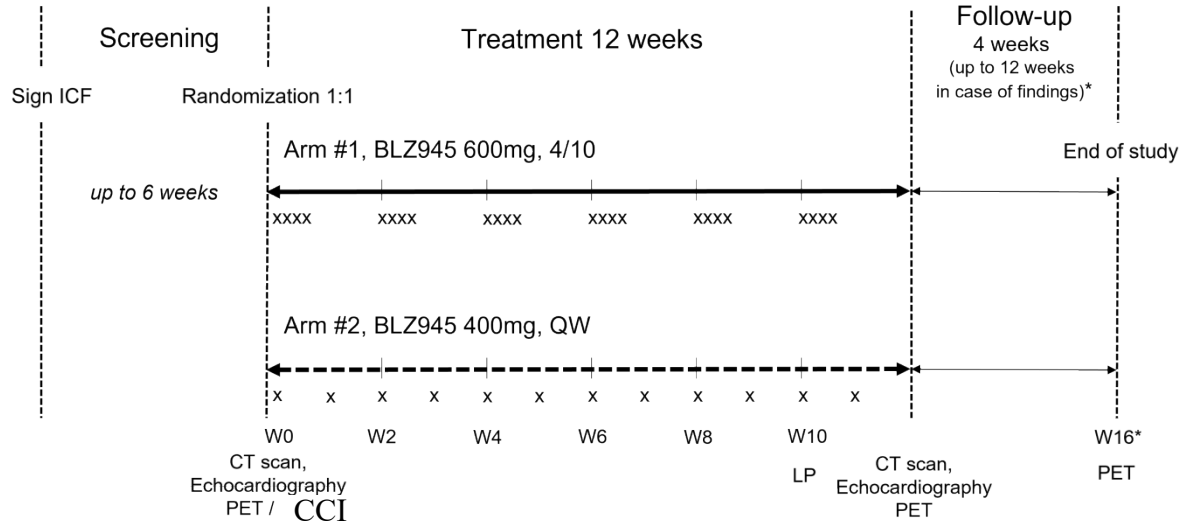
The cohort includes a screening period (up to 6 weeks), a 12-week treatment period, followed by a 4-week safety follow-up (Figure 3-4). Participants who completed the 12-week treatment period as per assessment schedule (Table 8-5) consent and are eligible, may continue to an additional 24-week extended treatment period on the same regimen (Figure 3-5).

Participants will be randomized in a 1:1 ratio across two dosing regimens: Arm #1: 600 mg BLZ945 in repeated cycles of 4 days on treatment followed by 10 days off treatment (4/10) or Arm #2: 400 mg BLZ945 once a week (QW).

Participants previously screened or dosed in Cohorts 1 to 4 may be enrolled in Cohort 5 if they meet eligibility criteria.

A PET sub-study will enroll approximately 8 participants at specific study sites. CCI

**Figure 3-4 Study design Cohort 5**



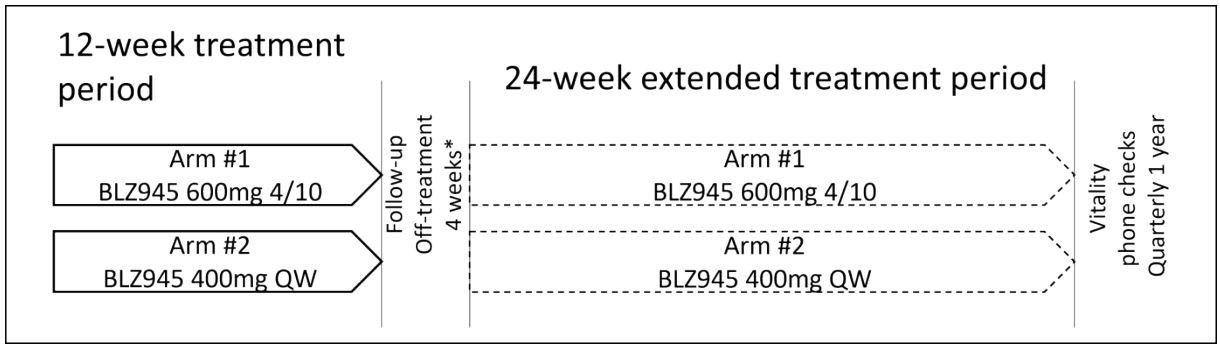

x = drug administration

W = week of treatment

* 4 weeks follow up in all participants + 8 weeks for recovery in participants with findings

# Cohort 5 Commercially Confidential Information PET sub-study will recruit approximately 8 participants at selected sites

**Figure 3-5 Study design Cohort 5 including the 24-week extended treatment period**




* 4 weeks follow up in all participants + 8 weeks for recovery in participants with findings

Each participant in Cohort 5 will undergo:

- The screening and baseline visit to assess eligibility
- The treatment period of 12 weeks
  The follow-up period without treatment for 4 weeks (and up to 12 weeks), including the end of study visit (EoS 1).

Participants who are eligible and willing to continue in the 24-week extended treatment period will receive additional treatment for 24 weeks and will be followed up for one year via phone calls.

All participants will undergo a CT-scan of the esophagus and an echocardiogram at screening after eligibility is confirmed from other screening visit assessments, and at Week 12 (End of Treatment 1). If a participant discontinues treatment before Week 4, the subsequent CT-scan and echocardiography planned at EoT1 visit (Week 12) do not need to be performed.

An additional safety follow-up visit with the corresponding procedure (CT scan or echocardiography or both) will be done at Week 24 in participants showing clinically relevant changes at Week 12. The additional safety follow-up visit at Week 24 will also be done in case of unresolved diagnosed vasculitis; during this visit, safety laboratory tests will be performed locally and blood for inflammatory markers of vasculitis will be collected.

The maximum study duration for each participant enrolled in Cohort 5, including the 6-week screening period, is 22 weeks, or 30 weeks if an additional safety follow-up visit has to be performed.

After the completion of the Follow up period (Week 16 visit), eligible participants will be offered to continue treatment with BLZ945 for an additional 24 weeks. The assessments conducted at Day 113 will be considered as the baseline assessment for the extended treatment period of 24 weeks, ie. up to Week 40. Participants will continue on the same dosing regimen during the extended treatment period. Participants who consent to enroll in the extended treatment period will be asked to return for safety, tolerability, CCI and functional assessments at regular visits as indicated in Table 8-7.

Participants who discontinue treatment during the extended treatment period will be asked if they agree to continue attending the study visits for assessments of safety and clinical function. After the end of the treatment period, quarterly telephone contacts for one year will be implemented to collect vital status information including survival, initiation of permanent assisted ventilation, and feeding tube utilization.

### PET sub-study

Participants in the PET sub-study will receive:

- An MRI at the end of screening period (after rs6971 genotype is known, and eligibility is confirmed from the other screening visit assessments) for delineation of the brain regions of interest (ROIs), through either stand-alone MRI or during PET/MRI scanning if PET/MRI is used. A maximum of three PET scans. These will include the baseline PET scan and two additional PET scans, which will be performed following repeated dose administration of BLZ945. The 2nd PET scan will be performed on Week 12 and the 3rd PET scan on Week 16. Refer to Table 8-5 for accepted visit windows.

  A transmission scan for attenuation correction will be acquired before each PET scan using an appropriate method [example: a $^{137}$Cs point source or a low dose CT scan depending on the PET system used, i.e., High Resolution Research Tomography (HRRT) or PET/CT ].
  - 1st PET Scan
    - In order for the participant to be eligible for the PET sub-study, the baseline PET scan (which is taken during screening period and at latest at baseline visit) must be of sufficient image quality to enable the measurement of Vt in the relevant brain regions.
  - 2nd and 3rd PET Scan
    - The participants will have a 2nd PET scan with [$^{11}$C]-PBR28 at Week 12 to assess microglial reduction.
    - The repopulation of microglia will be assessed during the 3rd PET scan at Week 16.

If the 2nd or 3rd PET scan cannot be performed on the planned day for any reason, the assessment can be scheduled per the visit windows stated in the assessment schedule.

### Remote Procedures

Cohorts 1-4: Participants may have the option for their study visits to occur on an outpatient basis in conjunction with home nursing on the visit days between PET scan 1 and 2. The remote procedures will be offered in certain countries and sites as determined by Novartis based on national and local regulations.

Cohort 5: Participants may have the option for selected study visits to occur on an outpatient basis in conjunction with home nursing during treatment period as per Table 8-5.

Home nursing will be implemented at the investigator's discretion and based on risk-benefit considerations of the participant's clinical condition.

Procedures will be performed remotely under the oversight of the Investigator, who retains accountability for the oversight and all efficacy and safety decisions with delegation of tasks to an off-site healthcare professional. The off-site nurses will be provided by a third-party vendor sourced by Novartis. Where a site wishes to use off-site nurses that are not provided by Novartis this must be agreed with Novartis before use.

# 4 Rationale

## 4.1 Rationale for study design

### 4.1.1 Rationale for study design for Cohorts 1-4

The study fits an Emax model to the TSPO binding reduction (as a measure of microglia reduction) data from all participants at Day 5 and it uses an informative prior derived from allometric scaling of mouse data. Further references to measures of change in microglia, in this protocol, refer to TSPO binding, which is considered a measure of microglial volume.

For this planned study, which is designed to evaluate changes in activated microglia pre- and post-treatment within an individual, a control arm is not needed and an open-label study design is appropriate. The dose levels and treatment duration of BLZ945 inducing microglial reduction are not known for humans, thus the testing of a range of possible dose levels and / or dosing durations may be required.

TSPO is expressed at low levels by glial cells and other cells in the healthy brain. However, its expression is highly upregulated during microglial activation (Banati 2002; Cagnin et al 2007; Chen, Guilarte 2008; Tronel et al 2017). TSPO PET imaging is the current gold standard technique for *in vivo* assessment of neuroinflammation and is widely recognized as a useful biomarker of activated microglia involvement in CNS disorders. Increased TSPO expression has been observed in brain regions of ALS subjects, such as motor cortex, compared to healthy controls (Turner et al 2004; Corcia et al 2012; Zürcher et al 2015). The PET tracer [$^{11}$C]-PBR28 is a second generation TSPO radioligand that has been used widely to measure microglial activation in neurodegenerative diseases, including ALS. It shows higher affinity, superior signal-to-background ratios and more favorable pharmacokinetics than the first generation radioligand ([$^{11}$C]-PK-11195). It is sensitive to the rs6971 polymorphism in the TSPO gene and, therefore, genetic stratification is required to exclude low-affinity binders (LAB), which would correspond to less than 10% of the population (Owen et al 2012; Kreisl et al 2013; Turkheimer et al 2015).

In human studies using PET, both the total number of participants and the number of scans per participant are limited. For this study, the number of participants is limited to approximately 20 and the number of PET scans is limited to up to 3 for each participant. The study will be conducted using an adaptive design to best characterize the exposure–time–PD relationship. Adaptive-optimal designs can provide an efficient experimental design for studies using PET, by minimizing the number of participants and maximizing the information obtained.

For Cohorts 1 to 4 of this study, 16 participants with ALS were enrolled to achieve the primary objective of the study. The screening/baseline PET scan is needed to assess binding of [$^{11}$C]-PBR28 to the TSPO receptor, which enables quantification of activated microglia before treatment with BLZ945. During the subsequent scans, changes in the binding of [$^{11}$C]-PBR28 in the brain will allow for an indirect measurement of the changes in the amount of activated microglia. Arterial blood samples will be drawn during the PET scanning procedures to define the metabolite-corrected arterial plasma input function that will be used for quantification of the PET data. Quantitative analysis with tracer kinetic modelling and arterial input function is the gold standard.

Due to the requirement of frequent blood sampling for PK evaluations during the dosing period, participants should be domiciled from Day -1 until the day after last dosing. However, participants may have the option for their visits to occur on an outpatient basis in conjunction with home nursing. In this situation, home nurses may be able to carry out study activities on the visit days between PET scan 1 and 2. Having participants domiciled at the study center or allowing them to be at their residence along with home-nursing will facilitate the timely collection of these samples and decrease the travel requirements of study participants. If no clinically significant AEs are observed at Day 5 in case of a 4-day dosing (or Day 8 for 7 days dosing), participants will be allowed to leave the center.

### 4.1.2 Rationale for study design for Cohort 5

In the previous cohorts, study participants received a single cycle of BLZ945 using a 4/10 dosing regimen. TSPO PET imaging data from Cohorts 2 to 4 indicated a decline, compared to pre-dose, in TSPO PET signal following dosing with BLZ945 in the majority of study participants and was still observed at 10 to 15 days off drug. In contrast, peripheral monocyte counts returned to baseline by 10 days off drug. This suggests that repeated cycles could result in additional TSPO PET signal changes, reflective of brain microglial reduction, while allowing for the recovery of peripheral monocyte macrophage lineage cells. Since the depletion of peripheral monocyte macrophage lineage cells is an undesirable on-target effect of BLZ945, a longer effect centrally could result in a more favorable treatment profile. Cohort 5 will therefore extend the duration of treatment to 12 weeks to evaluate the safety and preliminary efficacy of repeated cycles of BLZ945, using two dosing regimens. Additional safety monitoring assessments based on preclinical data, as well as new clinical and PD outcome measures have been added in order to evaluate the safety and efficacy of BLZ945 administered in these repeated cycles.

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Participants will receive a maximum of 72 doses (for the treatment arm #1, 4/10) and 36 doses (for the treatment arm #2, QW) during the entire treatment period of 40 weeks.

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### 4.1.3 Rationale for choice of background therapy

With the exception of the prohibited medications described in Section 6.2.2, the participants can continue on their usual care treatment, according to the treating physician and local guidelines.

To date there are three approved drugs in the US for the treatment of ALS, riluzole, edaravone and sodium phenylbutyrate/taurursodiol. These three drugs are not approved globally. Only riluzole is currently approved in the EU and is therefore considered an AxMP per EU Clinical Trial Regulation 536/2014. It is expected that a large proportion of the participants enrolled in the study will be under one of these ALS treatments.

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The metabolism of riluzole is mostly hepatic and consists of cytochrome P450-dependent hydroxylation (phase I reaction) and glucuronoconjugation (phase II reaction) (Sanderink et al 1997). The primary metabolic pathways of riluzole biotransformation in humans may involve direct glucuronidation of riluzole (involving the glucurotransferase isoform UGT-HP4) and oxidation of riluzole to N-hydroxyriluzole by CYP1A2 and CYP1A1, followed by rapid glucuronidation. Furthermore, riluzole was shown to be a substrate for breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp) (Milane et al 2009). BLZ945 was identified in vitro as an inhibitor of CYP1A1 and of transporters P-gp and BCRP.

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Phenylbutyrate/taurursodiol is available as oral therapy. It is a fixed combination of sodium phenylbutyrate and taurursodiol. No mass balance studies of sodium phenylbutyrate and taurursodiol have been conducted in humans to confirm the metabolic pathways and elimination routes. Sodium phenylbutyrate/taurursodiol is a substrate of OATP1B3. Sodium phenylbutyrate/taurursodiol inhibits CYP2C8 and induces CYP3A4 based on *in vitro* data

(Relyvrio US product information). BLZ945 is an inhibitor of OATP1B3 but static modeling showed no DDI risk at 800 mg dose of BLZ945. Commercially Confidential Information

Edaravone is available as intravenous or oral therapy. Glucuronide conjugation is the primary pathway for edaravone metabolism and eight UGTs (UGT1A1, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B7, and UGT2B17) were found to contribute to the production of a significant amount of glucuronide metabolites (Dash et al 2018). The findings from in vitro studies demonstrated that, at a clinical dose, edaravone and its metabolites are not expected to potentially inhibit CYP enzymes, UGTs and transporters in humans. The pharmacokinetics of edaravone are not expected to be significantly affected by inhibitors of CYP enzymes, UGTs, or major transporters (Radicava US product information).

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In case of approval of new ALS treatments, the same restrictions as defined for eligibility will be applied (see Section 5.1). Such therapies are expected to be maintained throughout the study duration unless discontinued for medical reasons. Initiation of additional ALS treatment during the study is prohibited.

Treatment-naive participants should only be enrolled if, in the opinion of the investigator, they can refrain from initiation of an additional approved ALS treatment throughout the course of the study.

## 4.2 Rationale for dose/regimen and duration of treatment

### 4.2.1 Dosing rationale for the first four cohorts (Cohort 1 - 4)

The starting dose for BLZ945, for participants enrolled in this trial, is set at 300 mg p.o. administered once daily for 4 days.

The first in human study with BLZ945 (CBLZ945X2101), is currently ongoing in adult participants with advanced solid tumors. The Investigator's Brochure (IB) contains a description of the relevant clinical experience from study CBLZ945X2101 with dosing up to 1200 mg per day with a 4 days on/10 days off dosing regimen. The current study will employ similar doses and dosing regimens as used in the ongoing study CBLZ945X2101 and described in the IB.

This dosing regimen of 4 days on/10 days off (4/10) has been established to control asymptomatic AST/ALT increase, which is believed to be an on target effect due to reduced clearance of these circulating transaminases resulting from a drug-induced decrease in Kupffer cells, which are also reduced by CSF-1R inhibition. The safety data from the FIH study (CBLZ945X2101) has been carefully reviewed to identify a safe starting dose for administration to ALS participants. In the ongoing CBLZ945X2101 study, eight participants were enrolled and treated at the planned starting dose for this study in ALS participants, (300 mg, 4 days on/10 days off, BLZ945). None of the treated participants experienced any dose limiting toxicity (DLT).

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The BLZ945 PK in ALS participants was predicted based on preliminary PK data in study CBLZ945X2101 (assumes similar PK in ALS participants to that in oncology participants). Commercially Confidential Information

The results of the PK/PD modeling indicate that 4 days of treatment with the selected starting dose of 300 mg BLZ945 once daily is predicted to result in a reduction of 10-12% in brain microglia. In the FIH study (CBLZ945X2101), preliminary PK data indicated that BLZ945 AUC0-24h and Cmax following a 300 mg once daily administration for 4 days, were between 3.42- and 7.4-fold and between 2.7- and 6.7-fold lower, respectively, Commercially Confidential Information

A starting dose of 300 mg has been chosen, since it is lower than the current dose being evaluated in the FIH study, CBLZ945X2101. The first cohort will be dosed for 4 days to follow the FIH dosing schedule. Dosing will continue according to the dose escalation schedule shown in Figure 3-2.

The radiotracer [$^{11}$C]-PBR28 will be injected as a bolus of approximately 350 MBq i.v. PET radiotracers are administered in very low concentrations, which allow for detection of ligand-target interactions without prompting a pharmacological effect. According to published data, [$^{11}$C]-PBR28 can be prepared at a sufficiently high specific activity and an injection of 350 MBq will permit determination of activated microglia (Scott et al 2018; Zürcher et al 2015; Alshikho et al 2016).

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### 4.2.2 Dosing rationale for Cohort 5

Several BLZ945 dosing regimens were explored in a previous oncology study in patients with advanced solid tumors, including glioblastoma (CBLZ945X2101). In the CBLZ945X2101 Phase I/II study conducted in adult participants with advanced solid tumors, 192 patients have been exposed to BLZ945 as single agent or in combination with PDR001. In patients exposed to BLZ945 single agent, the median duration of treatment was 8.0 weeks (range: 1.0-161 weeks) in Phase 1 (n=80) and 9.9 weeks (range: 2.0-68 weeks) in Phase 2 (n=22). In patients exposed to BLZ945 in combination with PDR001, the median duration of treatment was 8.0 weeks (range: 2.1-212 weeks) in Phase 1 (n=69) and 8.0 weeks (range: 1.9-27 weeks) in Phase 2 (n=21). In the CBLZ945X2101 study a maximal dose of 1600 mg was used with a QW regimen and a dose of 1200 mg in cycles of 4/10 was selected for further studies. The most frequently observed adverse events (≥ 10 %) that were suspected to be related to study drug were enzyme elevations (AST, ALT, CPK, amylase and lipase), nausea, vomiting, fatigue, and decreased appetite. For further details on study CBLZ945X2101, please see the IB.

Although dosing with 1600 mg/day with a QW regimen and 1200 mg/day with a 4/10 regimen, was tolerated in patients with advanced solid tumors, in patients with ALS, treated in Cohorts 1-4 of study CBLZ945C12201, an increased number of adverse events was seen at daily doses of 1200 mg, while dosing at 800 mg per day was generally well tolerated. Therefore, the 800 mg dose has been identified as the highest well-tolerated dose in patients with ALS. In Cohort 5, two dose-regimens (continuing repeated cycles of 4/10 vs QW dosing of BLZ945) will be used to evaluate the PD effects of BLZ945 up to end of treatment.

The 800 mg/day dose level was originally selected for both treatment arms in this Cohort. Of the first 12 participants enrolled in Cohort 5, 3 out of 6 who were randomized to the QW dosing regimen experienced adverse events of liver transaminase elevations >5 x ULN, one of whom was reported as serious. In an effort to reduce the likelihood of further liver enzyme elevations, for the remainder of the study, the dose will be reduced to 400 mg in the QW dosing arm. The 400 mg dose level closely corresponds to the lowest dose that has been previously administered to participants with ALS (300 mg) in Cohort 1 of this study.

Although similar adverse events of transaminase elevations were not seen in the 4/10 dosing arm, the observed tolerability with repeated dosing cycles of 4/10 at 800 mg was worse than had been seen with a single dosing cycle in Cohort 4. In Cohort 5, two of the six initial participants either discontinued treatment or required dose reductions due to poor tolerability. Therefore, in an effort to improve tolerability, the dose for the 4/10 regimen will be reduced to 600 mg. Fewer adverse events were observed at the 600 mg dose level than at the 800 mg dose in Cohorts 1-4.

The two dose regimens were selected in order to account for the expected accumulation of microglia reduction in the CNS with administration of repeated dosing cycles, while allowing for the recovery of the peripheral (non-CNS) monocyte macrophage lineage cells between dosing intervals, in order to reduce the risk of the undesired peripheral PD effects over repeated treatment cycles, such as liver enzyme elevation. In both regimens, the BLZ945 plasma levels are expected to decrease below the limit of quantification by the end of their respective "off" periods, in line with an apparent elimination $T_{1/2}$ of about 24h.

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Although the overall treatment duration in Cohort 5 of 36 weeks (12 weeks of treatment followed by 24 weeks extension) will formally exceed that of the 13-week repeat dose toxicity studies, treatment over this period will result in a maximum of 72 administrations of BLZ945 for the 4 days on/10 days off (4/10) dosing regimen and 36 administrations of BLZ945 for the 1 day on/6 days off (QW) dosing regimen. Therefore, the total number of administrations to participants will remain below the ≥91 administrations (consecutive daily dosing for 13 weeks) that were administered to the nonclinical species.

## 4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Not applicable.

## 4.4 Purpose and timing of interim analyses/design adaptations

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## 4.5 Risks and benefits

Because the potential therapeutic effects of BLZ945 are unknown, no clinical benefit to study participants is expected.

### Potential Risks Related to BLZ945

The study inclusion/exclusion criteria and prohibited medications have been chosen to exclude potential participants who are at a greater likelihood to suffer an adverse effect of BLZ945; safety monitoring measures have been implemented to mitigate risks to trial participants. In addition, an independent DMC will be reviewing individual and aggregated data from Cohort 5 throughout the 40 weeks of extended treatment on a regular basis for safety oversight.

*Effects on liver enzymes and creatine phosphokinase (CK)*

Reversible AST, ALT, and CK elevations may be expected with administration of BLZ945. In preclinical studies in rats and monkeys, increased serum ALT, AST and CK activities were observed at all doses. The transaminase elevations were reversible upon discontinuation of BLZ945 administration and were not associated with tissue damage on histological examination. Investigative studies showed that inhibition of the CSF-1 pathway reduces clearance of AST, ALT and CK without increased production or evidence of cellular damage, and that this change in clearance correlates with reduction in Kupffer cell numbers (Radi et al 2011, Pognan et al 2022). In the study conducted in adult participants with advanced solid tumors (CBLZ945X2101), asymptomatic increases in AST, ALT and CK were reported with BLZ945 monotherapy in the absence of liver or muscle injury.

In Cohort 5 of study CBLZ945C12201, to date, three participants have experienced significant elevations of AST / ALT (grades 3 and 4) in the weekly dosing regimen with 800 mg, including one potential case of Hy's Law. These events resolved approximately 1 month after the treatment cessation. Following the observation of these AST / ALT elevations, the study protocol was amended to reduce the dose of BLZ945 for future participants.

Participants with liver disease or abnormal liver chemistry will be excluded from the study (see details in Section 5.2). Safety monitoring for liver function, close observation and follow-up of liver abnormalities and stopping rules have been implemented to mitigate this risk.

*Effects on the GI tract*

GI events such as nausea, vomiting and diarrhea have been observed in the clinical study CBLZ945X2101.

In cohorts 1-4 of study CBLZ945C12201, commonly reported GI events included nausea, vomiting, diarrhea, abdominal pain; most of these events were observed in the 1200 mg dose group. A lower dose was selected for Cohort 5 to improve GI tolerability.

*Effects on bone*

In nonclinical studies, findings in bones consisted of thickened and/or dysplastic primary growth plate in rats and increased thickness of the physis in monkeys. They were reversible and are consistent with inhibition of osteoclasts (Dai et al 2002, Dobbins et al 2002). The impact of this potential risk in adults who no longer have active growth plates is currently unknown.

*Accumulation of extracellular matrix (ECM)*

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In addition, in the study conducted in adult participants with advanced solid tumors (CBLZ945X2101), while periorbital, orbital, eyelid, and face swelling has been observed after treatment with BLZ945, clinically significant adverse events related to ECM accumulation were not observed and

echocardiography measurements did not show changes in cardiac function associated with BLZ945 administration.

Participants with active GI conditions that could adversely affect esophageal function, cardiac and cardiac valve disorders will be excluded from this study (see details in Section 5.2). The planned Cohort 5 of this study includes an assessment of the potential for ECM accumulation on heart and cardiac valves (echocardiography) and on the esophagus (CT scan). In addition to the follow-up period will be extended up to Week 24 in the event of abnormalities on echocardiography or CT scan at Week 12. Participants with safety findings at Week 12 that prolong follow-up to Week 24 will not be eligible for entering the extension study.

*Vasculitis*

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Furthermore, no specific events indicating an impact on blood vessels were observed in the clinical study CBLZ945X2101. This suggests that vascular inflammation would be unlikely to occur in the current study using the planned doses and intermittent dosing regimens.

Participants with history of active vasculitis or autoimmune disease associated with vasculitis will be excluded from this study (see details in Section 5.2). Safety monitoring for vascular inflammation will include a detailed assessment of signs and symptoms of vasculitis (including guidance in the adverse event diary for the identification of signs and symptoms by the patient), detailed physical examination by the investigator or qualified delegate, laboratory assessments including markers of general inflammation (i.e., erythrocyte sedimentation rate and C-reactive protein), complete blood count, liver function tests, renal function tests (serum creatinine, blood urea nitrogen) and urinalysis for hematuria, proteinuria and cell casts.

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A detailed guidance for the identification of potential cases of vasculitis, clinical monitoring and management of suspected cases of vasculitis is provided in Section 16.3. Stopping rules for participants with confirmed vasculitis have been implemented and participants with signs of vasculitis will not be eligible to enter the extension study.

### 4.5.1 Potential risk associated with the COVID-19 Pandemic

Novartis is committed to supporting the safety and well-being of our study participants, investigators, and site staff. All local regulations and site requirements are being applied in the countries that are affected by the COVID-19 pandemic, including COVID-19 testing of participants. The Novartis clinical trial team will review the situation in each participating country and work with investigators to continue to ensure the safety of participants during the conduct of the trial. BLZ945 may have immunosuppressive effects; the required COVID-19 testing prior to dosing, and where home nursing is considered feasible, the risk for COVID-19 may be further reduced through the implementation of this option. These factors suggest there will be no additional risks related to COVID-19 for participants who enroll in this study. As the COVID-19 situation evolves, investigators must use their best judgement to minimize risk to participants during the conduct of the study. If participants (Cohorts 1-4) are diagnosed with COVID-19 during the treatment period, these participants should be discontinued and monitored accordingly. For participants enrolled in Cohort 5, refer to Section 6.5.2.

### 4.5.2 Potential risks associated with exposure to ionizing radiation

This clinical study involves exposure to radiation from the CT and PET examinations. These assessments are intended for research purposes only.

Radiation dose for participants from Cohorts 1-4:

- According to published dosimetry for [$^{11}$C]-PBR28 (Brown et al 2007), the total radiation from the PET scans will be approximately 6.93 mSv (693 mrem). This amount of radiation is equivalent to 2.3 years of exposure to background radiation (average yearly background dose is approx. 3 mSv in the US).
- If a low dose CT scan (PET/CT) is acquired for attenuation correction purposes, the total radiation exposure will be approximately 8.1 mSv (810 mrem), equivalent to 2.8 years of exposure to background radiation.

The carrier PBR28 mass that will be administered to each participant and each PET radiotracer injection is expected to be less than 1 µg and should not exceed 10 µg. Based on the literature (Brown et al 2007), i.v. injection of 650 MBq [$^{11}$C]PBR28 (carrier PBR mass of approx. 1.5 µg) produced no clinically observable effects.

Radiation dose for participants from Cohort 5:

- The total radiation dose from the esophagus CT scans will be approximately 8 mSv (800 mrem), equivalent to 2.7 years of exposure to background radiation.
- Those participants who will also be part of the PET sub-study will receive a total radiation dose of approximately 16 mSv (5.3 years of exposure to background radiation) from the esophagus CT and the PET assessments.

For effective radiation doses between 3 mSv (300 mrem) and 50 mSv (5000 mrem), the risk is considered to be minimal (Stabin 2022) or moderate (ICRP 1991). The radiation exposure in this study involves low to moderate risk. This is necessary to obtain the research information desired and is balanced against the substantial societal benefit gained from the trial.

### 4.5.3 Potential risks associated with arterial cannulation (Participants undergoing PET examinations)

Arterial line placement is considered a safe procedure, with a low rate of major complications. However, it is not entirely without risk. Arterial cannulation may cause mild-to-moderate pain, hematoma, inflammation, bleeding or bruising at the puncture site. It may also cause spasm or clotting of the artery with a temporary decrease in blood flow. In rare instances, blocking of the artery, tearing of the artery, arterial leakage, poor healing or infection at the site of the catheter insertion may occur.

Risks are minimized by having the procedure performed by an experienced physician. Pain is minimized by using a local anesthetic. Infection can be avoided by cleansing of the skin prior to catheter insertion.

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### 4.5.5 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of up to 8 weeks in Cohorts 1-4, up to 22 weeks for Cohort 5 and up to 40 weeks for extended treatment period of Cohort 5, from each participant as part of the study. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the assessment schedule (Table 8-1, Table 8-2, Table 8-3, Table 8-4, Table 8-5, Table 8-6 and Table 8-7).

A summary blood log is provided in the Site Operations Manual (SOM). Instructions for all sample collection, processing, storage and shipment information is also available in the SOM.

See the section on the potential use of residual samples (Section 8.5.2.2).

## 4.6 Rationale for Public Health Emergency mitigation procedures

During a public health emergency as declared by local or regional authorities e.g., pandemic, epidemic, or natural disaster, mitigation procedures to ensure participant safety and trial integrity may be implemented. Notification of the public health emergency as declared by local or regional authorities should be discussed among investigators and Novartis. All procedures adapted to the situation must be submitted, if required as per local regulations,

through a protocol amendment for approval by local or regional Health Authorities and Ethics Committees prior to implementation of mitigation procedures.

### 4.7 End of study definition

Study completion is defined when the last participant finishes their last study visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator.

## 5 Population

The study population will be comprised of adults who are at least 18 years old with clinically probable laboratory supported, or definite ALS according to the World Federation of Neurology Revised El Escorial criteria of either bulbar or limb onset (Ludolph et al 2015). A total of 16 participants were recruited in Cohorts 1-4. Cohort 5

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PET sub-study will recruit approximately 8 participants.

### 5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Cohorts 1-5: Able to communicate well with the investigator, to understand and comply with the study visits and procedures of the study.
2. Cohorts 1-5: Written informed consent must be obtained before any assessment is performed.
3. Cohorts 1-5: Male and female participants who are ≥ 18 years at screening, and who are diagnosed with familial or sporadic ALS according to the World Federation of Neurology Revised El Escorial criteria of either bulbar or limb onset.

4a. Cohorts 1-4: Able to swallow medication capsules, in the opinion of the investigator.

5. Cohorts 1-5: Disease duration from symptoms onset no longer than 48 months at the screening visit.
6. Cohorts 1-4 and Cohort 5 (PET sub-study): Having a SVC (slow vital capacity) equal to or more than 60% predicted normal value per local standards for gender, height, and age at the screening visit.

7a. Cohorts 1-5: Females of childbearing potential must have a negative pregnancy test at screening and/or baseline.

8a. Cohorts 1-4 and Cohort 5 (PET sub-study): High-affinity binders (HAB) to TSPO as evaluated by genotyping for the rs6971 polymorphism in the TSPO gene at the screening visit.

9. Cohorts 1-4 and Cohort 5 (PET sub-study): Baseline PET scan of sufficient image quality, as determined locally by the PET experts, to enable the measurement of [$^{11}$C]-PBR28 volume of distribution (Vt) in the relevant CNS regions.

10b. Cohorts 1-5: Treatment with approved ALS therapies is allowed, but participants need to be on a stable dose and regimen for at least 30 days prior to baseline. In case of riluzole, participants need to be on a stable dose and regimen for at least **90 days** prior to baseline.

In case for edaravone, the participant can be included if the initial BLZ945 dosing days can be scheduled in the off period of the edaravone treatment regimen.

11. Cohorts 1-4 and Cohort 5 (PET sub-study): An Upper Motor Neuron Burden (UMNB) scale ≥25 at the screening visit
12. Cohorts 1-4 and Cohort 5 (PET sub-study): BMI between 18-35 kg/$m^2$ at the screening visit.
13. Cohort 5 extended treatment period: Written informed consent for the extended treatment must be obtained before any assessment in the extended treatment period is performed.
14. Cohort 5 extended treatment period: Having completed the 12-week treatment period and the 4-week follow-up
15. Cohort 5 extended treatment period: Females of childbearing potential must have a negative pregnancy test at Week 16 and agree to continue the contraception methods used in the treatment period.

## 5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1a. Cohorts 1-5: A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities at screening or baseline
- QTcF > 450 msec (males)
- QTcF > 460 msec (females)

2. Cohorts 1-5: Active hematologic, hepatic, respiratory disorders that are clinically significant and may jeopardize the participant's safety if participating in the study or limit his/her participation in the study, including ability to tolerate the imaging studies.
3. Cohorts 1-5: Active dementia, neurologic diseases other than ALS, or psychiatric illness that in the opinion of the investigator would limit their participation in the current study.
4. Cohorts 1-5: Use of other investigational drugs within 5 half-lives of screening, or until the expected PD effect has returned to baseline, whichever is longer; or longer if required by local regulations.
5. Cohorts 1-5: History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes.
6. Cohorts 1-5: Presence of human immunodeficiency virus (HIV) infection based on screening lab results.

7a. Cohorts 1-5: Evidence of active or latent tuberculosis as assessed by Quantiferon or similar testing as per local practice at the screening visit.

8. Cohorts 1-5: Positive serology for hepatitis B surface antigen, or hepatitis C antibodies confirmed by an appropriate licensed test at screening.

9a. Cohorts 1-5: Signs or symptoms, in the judgement of the investigator, of a clinically significant systemic viral, bacterial or fungal infection within 30 days prior to the screening visit. COVID-19 specifically: testing as per local practice for COVID-19 will be completed within 3 days prior to first dosing. Positive COVID-19 test results would exclude participants from being enrolled into this study.

10a. Cohorts 1-5: Cardiac disorders, such as recent cardiac history (within 6 months of screening) of acute coronary syndrome, acute heart failure, or significant ventricular

arrhythmia at the screening visit or participants with a history of severe pulmonary hypertension, or cardiac failure class 3 or 4 of the NYHA classification, or history of reduced LVEF (<45%), or individuals with implanted cardiac pacemaker, or defibrillator.

11. Cohorts 1-5: Any of the following abnormal laboratory values at the screening visit:
    - Total white blood cell count (WBC) outside the range of 1,500-15,000/$mm^3$ (1.5 - 15.0 x $10^9$/L)
    - Platelets < 100,000/$mm^3$ (100 x $10^9$/L)
    - Hemoglobin (Hgb) < 8.0 g/dL (<0.5 mmol / L)
    - Lymphocyte count <500/$mm^3$ (<0.5 X $10^9$ / L)
12. Cohorts 1-5: Clinical evidence of liver disease or liver injury or any of the following hepatic conditions at the screening visit:
    - Active chronic liver or biliary disease
    - Direct bilirubin greater than the 1.5 x ULN
    - Alkaline phosphatase (AP) greater than 3 x ULN
    - AST (SGOT), ALT (SGPT) greater than 3 x ULN
    - Gamma-glutamyl-transferase (GGT) > than 3 x ULN
13. Cohorts 1-5: Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 14 days after last dose of BLZ945. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.
    - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example, hormone vaginal ring or transdermal hormone contraception

    In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
14. Cohorts 1-5: Pregnant or nursing female participants
15. Cohorts 1-5: Sexually active males unless they use a condom during intercourse while taking the drug during treatment, for 14 days after stopping BLZ945 and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via semen.
16. Intentionally left blank; removed in amendment 02

17. Cohorts 1-4 and Cohort 5 (PET sub-study): Any contraindications to MRI, including but not limited to the following:
    - Brain Aneurysm Clip
    - Implanted cardiac pacemaker, pacemaker wires or defibrillator
    - Prosthetic heart valves
    - Cochlear implant
    - Ocular foreign body (e.g., metal shavings)
    - Implanted insulin pump
    - Tattoos (as determined by radiologist)
    - Known claustrophobia
18. Cohorts 1-5: Taking medications prohibited by the protocol (see Section 6.2.2 (Prohibited medication) or Table 6-4 (Prohibited medication/procedure))

19a. Cohorts 1-4 and Cohort 5 (PET sub-study): Any contraindications to the arterial line sampling, including but not limited to the following:
    - Thromboangiitis obliterans (Buerger disease)
    - Full or partial thickness burns over the cannulation site
    - Inadequate circulation to the extremity
    - Raynaud syndrome
    - Coagulopathy
    - Inadequate collateral flow
    - Infection at the cannulation site
    - Previous surgery in the area
    - Synthetic vascular graft in the area

20. Cohorts 1-5: History or presence of impaired renal function as indicated by clinically significantly abnormal creatinine or BUN and/or urea values, or abnormal urinary constituents (e.g. albuminuria) at the screening visit.

21a. Cohorts 1-5: Active suicidal ideation as measured by a response of “yes” on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS at screening, if this ideation occurred in the past 6 months; or “yes” on any item of the Suicidal Behavior section, except for the “Non-Suicidal Self-Injurious Behavior” question of that section if this behavior occurred in the past 2 years. A response of "Yes" to these questions is considered exclusionary at screening.

22a. Cohorts 1-5: History of drug abuse or harmful alcohol use within the 12 months prior to dosing within the judgement of the investigator and the below definition, or evidence of such abuse as indicated by the laboratory assays conducted during screening. Harmful alcohol use is defined as a history of, or current alcohol misuse/abuse, defined as “Five or more standard drinks on the same occasion on each of 5 or more days in the past 30 days prior to screening."

23. Cohorts 1-5: Inability or unwillingness to undergo repeated venipuncture or arterial cannulation, or in the opinion of the investigator, participant would be at an increased risk for adverse events related to these procedures.

24. Cohort 5: Active GI conditions such as Barrett's esophagus, achalasia, esophageal varices and active or history of esophageal cancer, pre-existing pancreatic disease at screening visit.
25. Cohort 5: History of active vasculitis or history of autoimmune disease autoimmune disease associated with vasculitis (e.g., RA, SLE, Sjögrens disease, scleroderma).
26. Cohort 5: History or active cardiac valve disorder, such as clinically significant stenosis or regurgitation (CTCAE grade ≥2), congenital valve disease, or other clinical condition that might affect cardiac valve function (excluding hemodynamically insignificant mitral valve prolapse).
27. Cohort 5: Use of systemic anticoagulation that cannot be temporarily paused before study procedures (LP, arterial line placement for PET scan)
28. Cohort 5 extended treatment period: Participants who are planning to initiate treatment with an additional approved ALS therapy in the next 24 weeks

29a. Cohort 5 extended treatment period: Clinically relevant changes* on CT scan or echocardiography, signs of vasculitis, or evidence of a significant medical condition meeting treatment discontinuation criteria at EoT1 or EoS1 visits even if finding has resolved at EoS1.

* Participants with ≤3mm mean increase in esophageal wall thickness compared to the baseline (pre-BLZ945 dose), as measured by CT scan who completed EoT1 under the previous protocol versions are eligible to the extended treatment period.

# 6 Treatment

## 6.1 Study treatment

The study drug is defined as single agent BLZ945. The study drug will be provided by Novartis.

All dosages prescribed and dispensed to participants and all dose changes during the study must be recorded on the Dosage Administration Record electronic Case Report Form (eCRF).

Details on the requirements for storage and management of study treatment, and instructions to be followed for participant numbering, prescribing/dispensing, and taking study treatment are outlined in the SOM.

In Cohorts 1-4 for the 4-day dosing schedule, participants should take BLZ945 daily for 4 days at approximately the same time each day in the morning. On days that PK samples are obtained, the participants should take BLZ945 during the clinic visit, or in the presence of the home nurse, after the pre-dose PK samples and prior to post-dose PK samples, when instructed by the study staff and/or home nurse.

In Cohort 5, participants should take BLZ945 in accordance with the regimen to which they were assigned upon randomization, at approximately the same time each day in the morning. On Day 1 for Arm #2 and Day 4 for Arm #1, participants should take BLZ945 as well as their additional ALS treatment(s) (e.g. riluzole or sodium phenylbutyrate/taurursodiol) during the clinic visit or in presence of the home nurse. The exact time of the BLZ945 and additional ALS treatment administration should be recorded.

Participants should take BLZ945 on an empty stomach (i.e., fast from food and drink, except water) at least 1 hour before or 2 hours after a meal. Also see Section 6.2.4.1 for dietary restrictions.

If vomiting occurs during the course of treatment or after the daily dose, participants should not take the study drug BLZ945 again before the next scheduled dose. If the participant vomits an intact dose immediately after dose administration, the Sponsor should be contacted for determination about repeat dosing.

In Cohort 5, participants are allowed to take BLZ945 via gastric feeding tube. Participants will receive instructions on how to prepare and administer BLZ945 from the study site staff. The route of BLZ945 administration will be recorded in the CRF.

### 6.1.1 Investigational and control drugs

**Table 6-1 Investigational drug**

| **Treatment Title** | **BLZ945** | **BLZ945** | **BLZ945** | **BLZ945** |
|---|---|---|---|---|
| **Treatment Description** | Cohorts 1-4<br>300 mg, 600 mg, 800 mg, 1200 mg daily | Cohorts 1-4<br>300 mg, 600 mg, 800 mg, 1200 mg daily | Cohort 5<br>400 mg weekly | Cohort 5<br>600 mg 4 days on/10 days off |
| **Type** | drug | drug | drug | drug |
| **Dose Formulation** | capsule | capsule | capsule | capsule |
| **Unit Dose Strength(s)** | 50 mg | 200 mg | 200 mg | 200 mg |
| **Dosage Level(s)** | 300 mg, 600 mg, 800 mg, 1200 mg daily | 300 mg, 600 mg, 800 mg, 1200 mg daily | 400 mg weekly | 600 mg 4 days on/10 days off |
| **Route of Administration** | oral | oral | oral/enteral infusion | oral/enteral infusion |
| **Use** | experimental | experimental | experimental | experimental |
| **IMP** | Yes | Yes | Yes | Yes |

#### 6.1.1.1 Decentralized Clinical Trial Model (US sites only)

The study medication and all required clinical study supplies may be distributed via direct-to-participant shipment, if needed to accommodate home nursing.

### 6.1.2 Additional study treatments

Background treatment with approved ALS therapies is allowed (see Table 6-2), but participants need to be on a stable dose and regimen for at least 30 days prior to baseline for sodium phenylbutyrate/taurursodiol and at least 90 days prior to baseline for riluzole. Background regimens have to be captured in the eCRF accordingly. For Cohort 5, the riluzole and sodium phenylbutyrate/taurursodiol background dose and regimen must remain

unchanged at least until Day 1 (Arm #2) or Day 4 (Arm #1) included. The riluzole and sodium phenylbutyrate/taurursodiol dose administration must be captured in the eCRF (and on the patient diary when applicable) on the day of, and on the day before PK samples are collected (see Table 8-6).

Initiation of new or additional ALS treatment during the entire treatment duration is prohibited.

Participants who are on a stable dose and regimen of an approved treatment for ALS should continue throughout the extended treatment period unless they need to discontinue for medical reasons. Participants who elect to initiate an additional approved ALS treatment during the 4-week follow up period, will not be eligible to participate in the extended treatment period.

**Table 6-2 Additional study treatment**

| **Treatment Title** | **riluzole** | **edaravone** | **edaravone** | **sodium phenylbutyrate/ taurursodiol** |
|---|---|---|---|---|
| **Treatment Description** | 50 mg, Q 12 hours | 60 mg, daily, Initial cycle: 14 days on, 14 days off Subsequent cycles: 10 days out of 14-day periods, followed by 14 days drug free period | 105 mg, daily, Initial cycle: 14 days on, 14 days off Subsequent cycles: 10 days out of 14-day periods, followed by 14 days drug free period | Initial dose: 3 g sodium phenylbutyrate and 1 g taurursodiol, daily for 3 weeks Maintenance: 3 g sodium phenylbutyrate/ 1 g taurursodiol, Q 12 hours |
| **Type** | drug | drug | drug | drug |
| **Dose Formulation** | tablet | solution | oral suspension | oral suspension |
| **Unit Dose Strength(s)** | 50 mg | 30 mg /100 mL | 105 mg/5 mL | 3 g sodium phenylbutyrate and 1 g taurursodiol |
| **Dosage Level(s)** | 100 mg, daily | 60 mg, daily | 105 mg, daily | Initial dose: 3 g sodium phenylbutyrate and 1 g taurursodiol, Maintenance: 6 g sodium phenylbutyrate/ 2 g taurursodiol Q 12 hours |
| **Route of Administration** | oral | intravenous infusion | oral/ enteral infusion | oral/ enteral infusion |
| **Use** | background intervention | background intervention | background intervention | background intervention |

| Treatment Title | riluzole | edaravone | edaravone | sodium phenylbutyrate/ taurursodiol |
|---|---|---|---|---|
| Authorization status of the AxMP in EEA | Yes | No | No | No |

Participants from European Economic Area (EEA) countries may receive only riluzole and participants from non-EEA countries may receive any ALS therapies approved in their country (riluzole, edaravone and/or sodium phenylbutyrate/ taurursodiol).

### 6.1.3 Treatment arms/group

Participants within a treatment cohort in Cohorts 1-4 all receive the same dose of BLZ945.

Participants in Cohort 5 will be randomized to receive either one or the other of the following treatment regimens:

- Treatment Arm #1 – 600 mg 4/10 dosing
- Treatment Arm #2 – 400 mg QW dosing

**Table 6-3 Treatment Arm(s)**

| Arm Title | Cohort 1-4 | Cohort 5 Treatment Arm #1 | Cohort 5 Treatment Arm #2 | Cohort 5 Treatment extension |
|---|---|---|---|---|
| Arm Type | Experimental | Experimental | Experimental | Experimental |
| Arm Description | Participants received BLZ945 300 mg (Cohort 1), BLZ945 600 mg (Cohort 2), BLZ945 1200 mg (Cohort 3), BLZ945 800 mg (Cohort 4) daily, for 4 days. | Participants will receive BLZ945 600 mg in repeated cycles of 4 days on treatment followed by 10 days off treatment (4/10) during 12 weeks, followed by a 4 week period off treatment. | Participants will receive BLZ945 400 mg once a week (QW) during 12 weeks, followed by a 4 week period off treatment. | Patients on Arm#1 and Arm#2 can enter an optional treatment extension period if eligible and will continue treatment at the same dosing regimen during 24 weeks. |
| Associated Treatment Labels | BLZ945 | BLZ945 | BLZ945 | BLZ945 |

## 6.2 Other treatment(s)

### 6.2.1 Concomitant therapy

The participant must be instructed to notify the investigational site about any new medications, herbal remedies and dietary supplements he/she takes after the start of the study treatment.

The participant may need concomitant medication(s) to tolerate the PET and/or MRI scans. Any concomitant medications used for this purpose must be documented accordingly.

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant is enrolled into the study must be recorded on the appropriate Case Report Forms. Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before enrolling a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

#### 6.2.1.1 Permitted concomitant therapy requiring caution and/or action

The following medications are to be used with **caution** in this study and only after discussion and alignment with the study sponsor:

1. Concomitant medications, which are known to be moderate inhibitors or inducers of CYP3A4/5 or CYP2C8, are permitted to be used with caution but not in combination. Refer to the SOM for permitted medications that require caution when concomitantly used with study drug.
2. Concomitant medications which are known to be narrow therapeutic index substrates of CYP3A4 and/or CYP2C8, are permitted to be used with caution. Refer to the SOM for permitted medications that require caution when concomitantly used with study drug.
3. Concomitant medications which are known to be substrates of OATP1B1, OATP1B3, P-gp, BCRP, OCT1, OCT2, OAT3, MATE1, or MATE2-K (with the exception of the narrow therapeutic index substrates of P-gp and BCRP which are prohibited - see Table 6-4), are permitted to be used with caution. Refer to the SOM for permitted medications that require caution when concomitantly used with study drug.
4. Drugs that alter the pH of the upper GI tract (e.g., H2-receptor antagonists, antacids) may alter the solubility of BLZ945 and reduce its bioavailability. Short-acting gastric acid modulators containing aluminum hydroxide and magnesium hydroxide, (e.g., Maalox®) or calcium carbonate (e.g., TUMS®) can be taken. However, it is recommended to take these drugs at least 1 hour before or 2 hours after administration of BLZ945. H2 receptor antagonists should be **avoided**. If participants are using H2 receptor antagonists (e.g., ranitidine or famotidine) during the course of this study, participants should take BLZ945 at least 3 hours before H2 receptor antagonists. In addition, next dose schedule of BLZ945 administration should be at least 6 hours after taking H2 receptor antagonists.

If any of these medications were taken without prior sponsor consultation, the sponsor needs to be consulted before the next dose.

5. Anti-platelet therapies are permitted to be used following discussion and approval by sponsor.

### 6.2.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed during the indicated period.

**Table 6-4 Prohibited medication/procedure**

| Medication | Prohibition period | Action to take in case prohibited medication taken |
|---|---|---|
| • Proton pump inhibitors. Examples include: omeprazole, pantoprazole, and lansoprazole | 1 week before treatment start until 4 days after last BLZ945 dosing, inclusive. | Discontinue study treatment and inform immediately sponsor |
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| • Narrow therapeutic index substrates of PgP and/or BCRP transporters | From the day of first BLZ945 dosing until 4 days after last BLZ945 dosing, inclusive | Discontinue study treatment and inform immediately sponsor |
| • Sensitive dual substrate of both BCRP and OATP1B | From the day of first BLZ945 dosing until 4 days after last BLZ945 dosing, inclusive | Discontinue study treatment and inform immediately sponsor |
| • Concomitant medications with known risk of QT prolongation*<br>• Hepatotoxic agent (e.g., allopurinol, methyldopa, sulfasalazine)<br>• Any investigational treatment related or not to ALS<br>• Hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF) and thrombopoietin mimetics<br>• Therapeutic monoclonal antibodies and immunosuppressive medication<br>• Systemic steroid therapy and other immunosuppressives<br>• Live vaccines | From screening until 4 days after last dosing, inclusive. | Discontinue study treatment and inform immediately sponsor |
| • Study drugs, devices, chemotherapy, or any other therapies that may modulate immune responses, including inhibitors colony | Depends on immunomodulatory treatment | To discuss with the Sponsor |

| Medication | Prohibition period | Action to take in case prohibited medication taken |
|---|---|---|
| stimulation factor 1 Receptor (CSF-1R) | | |
| • Anticoagulants | Cohorts 1-4: At least 5 half-lives before the first PET scan until after the last PET scan has been performed<br>Cohort 5: Anticoagulant therapies can be permitted for use following discussion and prior approval by sponsor | To discuss with the Sponsor |
| • Anti-platelet agents including acetylsalicylic acid (ASA) | Cohorts 1-4: 1 week before the first PET scan until after the last PET scan has been performed<br>Anti-platelet therapies can be permitted for use following discussion and prior approval by sponsor<br>Cohort 5: Can be used with caution if permitted by local practice, or following discussion with the sponsor, prior to the placement of the arterial line required for the TSPO PET procedure, and prior to the LP procedure in the other participants. | To discuss with the Sponsor |
| • Initiation/addition of approved ALS treatment | From screening until End of Study. | To discuss with the Sponsor |
| • Procedure: gastrojejunostomy or jejunostomy tube | From screening until End of Study. | Discontinue study treatment and inform immediately sponsor |

If the participant cannot discontinue a prohibited concomitant medication, the participant may be eligible if the participant has been on a stable dose for 3 months, AND Sponsor approval has been confirmed.

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See the SOM for a list of generic names of strong and moderate inducers or inhibitors of CYP3A4/5 and CYP2C8, and substrates of transporters OATP1B1/1B3, PgP and BCRP, as well as medications with known risk of QT prolongation.

### 6.2.3 Rescue medication

There is no known rescue medication. However, in the event of a hypersensitivity reaction, treat with appropriate therapy as outlined in the Site Operations Manual.

### 6.2.4 Restriction for study participants

For the duration of the study, participants should be informed and reminded of the restrictions outlined in this section.

#### 6.2.4.1 Dietary restrictions

- Cohorts 1-5: Participants must avoid consumption of Seville orange (bitter orange) (and juice), grapefruit or grapefruit juice, grapefruit hybrids, pomelos and star citrus fruits at least 7 days prior to the first dose of study treatment and until 4 or 7 days included after last dosing due to potential CYP3A interaction.
- Cohorts 1-4: In order to avoid wide variations in urine volumes on PK collection days, participants should be encouraged to have a fluid intake of approximately 240 mL every 4 hours during their waking hours, in addition to the fluid taken with meals and medication on Days 1 and 4 (in case of 4 days dosing) or Days 1 and 7 (in case of 7 days dosing).

#### 6.2.4.2 Other restrictions

Not applicable.

## 6.3 Participant numbering, treatment assignment, randomization

### 6.3.1 Participant numbering

The subject number assigned to a participant at screening remains the unique identifier for the participant throughout the study. For information on subject numbering, please see ‘subject numbering’ section in the Site Operations Manual.

### 6.3.2 Treatment assignment, randomization

No randomization will be performed in the first four cohorts of this study. The assignment of a participant to a particular cohort will be coordinated between the sponsor and sites.

In Cohort 5, participants will be randomized across the two study arms with a randomization ratio of 1:1.

Upon signing the informed consent form by the participant, the investigator or his/her staff will contact the IRT and provide the requested identifying information to register a subject into the IRT. If participant is eligible for the PET sub-study, results from the genotyping for rs6971 polymorphism in the TSPO gene high-affinity binders (HAB) to TSPO will need to be available prior to randomization.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A randomization list will be produced by or under the responsibility of Novartis Global

Clinical Supply using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio.

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

Follow the details outlined in the Site Operations Manual regarding the process and timing of treatment assignment and randomization of participants.

## 6.4 Treatment blinding

Not applicable.

## 6.5 Dose escalation and dose modification

### 6.5.1 Dose escalation guidelines for Cohorts 1-4

Prior to dose changes or dose regimen changes, data review of all safety/tolerability, PK data (as applicable) and PD up to 10 days after last treatment for all participants in the dose cohort will be performed, and must be assessed as satisfactory to proceed. The decision to proceed to the next dose or dose regimen will be made jointly between the Sponsor and the Investigator(s).

#### Data to be reviewed for modification of dose or dose regimen

The dataset that will be evaluated for dose escalation/de-escalation or dose regimen extension decisions, in between cohorts, will include the following data up until 10 days after last treatment: adverse events, safety laboratory assessments, vital signs, relevant findings on physical and neurological examinations, C-SSRS, ECG data, urine analysis, PK (as applicable. Refer to Section 3 for more information), PET imaging data.

#### Criteria for dose escalation

The sponsor and site investigators will perform a joint data review of safety data to assess the nature of any adverse events and decide upon study continuation with the next cohort.

In this study, after a minimum of 3 participants have completed Day 5 in the 4-day cohort or Day 8 in the 7-day cohort, safety must be reviewed and assessed as satisfactory to proceed to the next cohort.

Dose escalation decisions will be made by Investigators and Novartis study personnel. Decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study including safety information, and all PK (as applicable. Refer to Section 3 for more information), and PD data from evaluable participants.

Dose escalation or dose regimen modification will proceed according to the schema illustrated in Figure 3-2. Refer to Section 3 for more information. Dosing will continue until the maximum planned dose is reached unless a cohort or study stopping rule is met (see Section 9.1.4).

#### 6.5.1.1 Starting dose

The starting doses for BLZ945 will be 300 mg/day for 4 days for Cohort 1.

#### 6.5.1.2 Provisional dose levels

Table 6-5 describes the starting dose and the dose levels that are planned for Cohorts 1 to 4 in this trial. A total of five cohorts are planned (300 mg, 600 mg, 1200 mg daily for four consecutive days plus two additional cohorts at doses to be determined). Refer to Section 3 for more information regarding selection of dosing regimen for cohorts.

**Table 6-5 Provisional dose levels**

| Dose level | Proposed daily dose* | Increment from previous dose |
|---|---|---|
| -1** | 150 mg | -50% |
| 1 | 300 mg | (starting dose) |
| 2 | 600 mg | 100% |
| 3 | 1200 mg | 100% |
| 4 | 800 mg | -33% |
| 5 | 400 mg | -50% |
| 6 | 200 mg | -50% |

*It is possible for additional and/or intermediate dose levels to be added during the course of the study. Cohorts may be added at any dose level below the MTD in order to better understand safety, PK, or PD.

**Dose level -1 represents treatment doses for participants requiring a dose reduction from the starting dose level. No dose reduction below dose level -1 is permitted for this study.

### 6.5.2 Dose reductions/interruptions (Cohort 5)

#### Safety or tolerability issues

In case of safety or tolerability issues, the BLZ945 dose can be lowered in steps of 200 mg (1 capsule) per day. BLZ945 dosing may be interrupted for a maximum of four weeks for tolerability issues. Dosing can be restarted at the discretion of the investigator upon resolution, at the next lower dosing level (for example 400 mg or 200 mg). Once lowered for tolerability reasons, the dose should not be increased again.

Please see Section 16.1 for drug interruption and discontinuation rules in case of liver enzyme elevations.

#### COVID and other significant infections

A participant who develops clinical symptoms of COVID-19 or other significant infection should temporarily interrupt dosing until resolution of symptoms.

## 6.6 Additional treatment guidance

### 6.6.1 Treatment compliance

Cohorts 1-4: The administration of BLZ945 will be conducted on site and witnessed by study personnel, or at the participant's home and witnessed by the home nurse.

Cohort 5: The administration of BLZ945 will be performed on site during Day 1 or Day 4 if on-site visits or in the presence of home nurse at the participant`s home if this visit is a home nursing visit. Participants will be provided with a diary to capture date and time of study treatment intake and riluzole and/or sodium phenylbutyrate/taurursodiol administration (Section 8.5.6).

The data on study drug and any other potential therapy will be collected, in order to provide information about exposure and compliance. These data should correspond to the information requested on the standard CRFs. PK parameters will be determined in participants treated with BLZ945 as feasible, as detailed in pharmacokinetics section (Section 8.5.1).

### 6.6.2 Recommended treatment of adverse events

At present there is insufficient information to provide specific recommendations regarding treatment of adverse events (AEs).

The emergence of immune-related AE (irAE) may be anticipated based on general experience in clinical studies with similar class of compounds that block the negative immune regulators or interfere with immune cell compartments.

An irAE is a clinically important AE of unknown etiology associated with the study drug exposure. irAEs are typically low grade and self-limited, often occurring after multiple doses, and most frequently involving the GI tract (diarrhea/colitis), skin (rashes), liver (hepatitis), and endocrine systems (a variety of endocrinopathies). Serologic and immunological assessments should be performed as deemed appropriate by the Investigator, to verify the immune-related nature of the AE, and exclude an infectious or metabolic origin of the AE.

Medication used to treat AEs must be recorded on the appropriate CRF.

### 6.6.3 Emergency breaking of assigned treatment code

This section is not applicable since there is no blinding involved.

## 6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under the investigational and control drugs section (Section 6.1.1).

BLZ945 will be administered orally to the participant. See the Site Operations Manual for further details.

# 7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent. A separate informed consent will be signed for continuation in the Cohort 5 24-week extended treatment period.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

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During the COVID-19 pandemic that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference). Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately

documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

The study includes the option for the participant (at some sites) to have certain study procedures performed off-site by an off-site healthcare professional instead of at the study site. A separate home nursing document may be used in addition to the main ICF if a patient opts for home nursing. It is required as part of this protocol that the Investigator presents this option to the participant, as permitted by national and local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

Refer to the Site Operations Manual for a complete list of ICFs included in this study.

# 8 Visit schedule and assessments

Assessment schedules (Table 8-1 for 4 days dosing, Table 8-3 for 7 days dosing, Table 8-5 for Cohort 5 and Table 8-7 for the Cohort 5 extended treatment period) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1 for 4 days dosing, Table 8-3 for 7 days dosing, Table 8-5 for Cohort 5 and Table 8-7 for Cohort 5 extended treatment period) or as close to the designated day/time as possible. Refer to timing and preferred order of assessments in the SOM. Missed or rescheduled visits should not lead to automatic discontinuation.

**Table 8-1 Assessment Schedule, 4 Days dosing cohorts**

| **Period** | **Screening** | | **Treatment** | | | | | **Follow-up** | | | | **EOS** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | **Screening** | **Baseline[22]** | **Treatment[24]** | | | | | **Follow-up** | | | | **EOS** |
| **Visit Numbers[1]** | **1** | **20** | **100** | | **110** | **120** | **130** | **140** | **150[23]** | **160[23]** | **170[23]** | **1999** |
| **Days** | **-42 to -2** | **-1** | **1** | | **2** | **3** | **4** | **5 +1** | **8 ±2** | **14 ±2** | **19 ±2** | **36 ±2** |
| **Time (post-dose)** | **-** | **-** | **-** | **Pre-dose** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** |
| Informed consent | X | | | | | | | | | | | |
| Commercially Confidential Information | | | | | | | | | | | | |
| Inclusion / Exclusion criteria | S | S | | S | | | | | | | | |
| Study completion information | | | | | | | | | | | | X |
| Demography | X | | | | | | | | | | | |
| Detailed Medical History / Current Medical Condition[2] | X | | | | | | | | | | | |
| Hepatitis screen[3] | S | | | | | | | | | | | |
| Alcohol Test and Drug Screen [3] | S | | | | | | | | | | | |
| HIV screen[3] | S | | | | | | | | | | | |
| Quantiferon testing [3] | S | | | | | | | | | | | |

| Period | Screening | | Treatment | | | | | Follow-up | | | | EOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Name | Screening | Baseline[22] | Treatment[24] | | | | | Follow-up | | | | EOS |
| Visit Numbers[1] | 1 | 20 | 100 | | 110 | 120 | 130 | 140 | 150[23] | 160[23] | 170[23] | 1999 |
| Days | -42 to -2 | -1 | 1 | | 2 | 3 | 4 | 5 +1 | 8 ±2 | 14 ±2 | 19 ±2 | 36 ±2 |
| Time (post-dose) | - | - | - | Pre-dose | - | - | - | - | - | - | - | - |
| Covid-19 PCR testing[25] | S | S | | | | | | | | | | |
| Pulse rate | X | | | | | | | X | | | | X |
| Blood Pressure | X | | | | | | | X | | | | X |
| Body Temperature | X | | | | | | | X | | | | X |
| Body Height | X | | | | | | | | | | | |
| Body Weight | X | | | | | | | | | | | |
| Physical Examination | S | | | | | | | | | | | S |
| Fertility assessment[4] | S | | | | | | | | | | | |
| Targeted Neurological Examination[2] | S | | | | | | | | | | | S |
| ALS Functional Rating Scale Revised (ALS-FRS-R) | | X | | | | | | | | | | X |
| Slow Vital Capacity (SVC)[5] | S | | | | | | | | | | | |
| Upper Motor Neuron Burden Scale (UMNB) | X | | | | | | | | | | | X |
| Columbia-Suicide Severity Rating Scale (C-SSRS) [6] | X | | | | | | | X | X[7] | X[7] | X[7] | X |
| Hematology | X | | | X | X | X | X | X | X[7] | X[7] | X[7] | X |
| Clinical Chemistry | X | | | X | X | X | X | X | X[7] | X[7] | X[7] | X |
| Urinalysis | X | | | | | | | X | X[7] | X[7] | X[7] | X |
| Thyroid Function Test: T3, T4, TSH | S | | | | | | | | | | | |
| Coagulation Panel | X | | | | | | | | | | | |
| Electrocardiogram (ECG)[8] | X | | | X | X | X | X | X | X[7] | X[7] | X[7] | X |
| Pregnancy test[9] | S | S[10] | | | | | S | | S[7,10] | S[7,10] | S[7,10] | S |

| Period | Screening | | Treatment | | | | | Follow-up | | | | EOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Name | Screening | Baseline[22] | Treatment[24] | | | | | Follow-up | | | | EOS |
| Visit Numbers[1] | 1 | 20 | 100 | | 110 | 120 | 130 | 140 | 150[23] | 160[23] | 170[23] | 1999 |
| Days | -42 to -2 | -1 | 1 | | 2 | 3 | 4 | 5 +1 | 8 ±2 | 14 ±2 | 19 ±2 | 36 ±2 |
| Time (post-dose) | - | - | - | Pre-dose | - | - | - | - | - | - | - | - |
| Study drug administration | | | X | | X | X | X | | | | | |
| Participants domiciled[11,12] | | X | X | X | X | X | X | X[21] | | | | |
| PK blood collection (BLZ945) | See table below | | | | | | | | | | | |
| Commercially Confidential Information | | | | | | | | | | | | |
| PK urine collection (BLZ945) | | | X[14] | | | | X[14] | | | | | |
| Polymorphism rs6971 Genotyping | X | | | | | | | | | | | |
| CYP2C8 Genotyping | X[15] | X[15] | | | | | | | | | | |
| Commercially Confidential Information | | | | | | | | | | | | |
| PET scan | X[17] | X[17] | | | | | | X[18] | X[19] | X[19] | X[19] | |
| Arterial Blood Collection | X[17] | X[17] | | | | | | X | X[7] | X[7] | X[7] | |
| Brain MRI[20] | X | | | | | | | | | | | |
| Adverse Events | X | | | | | | | | | | | |
| Concomitant medications | X | | | | | | | | | | | |

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Visit structure given for internal programming purpose only
[2] Please refer to the SOM for more details.
[3] Screening test is done in local lab only.
[4] Only for women - Historical documentation is also acceptable; see section Pregnancy and assessments of fertility (in Section 8.4.3).
[5] Historical documentation of max 3 months old is also acceptable.
[6] The Columbia-Suicide Severity Rating Scale (C-SSRS) also needs to be performed at any unscheduled visit.
[7] For 300 mg cohort, participants should return for Day 14 assessments with the exception of the 3rd PET scan. For other cohorts, this assessment is only to be performed at the time of the 3rd PET scan.
[8] During the study, 12-lead ECGs should be conducted prior to blood collection.
[9] Serum pregnancy test result needs to be available and negative before dosing of the PBR28 tracer for the PET scan and the first BLZ945 dosing.
[10] The serum pregnancy test is preferred prior to each planned PET scan. Site can perform PET scan if result of urine pregnancy test within 24 hours of PET scan is negative, and local practice allows.
[11] Participants may have the option of home nursing during study days 1-4.
[12] Percent consumption of meals need to be recorded during the domiciliation period or during the period that the participants are having home nursing visits.
[13] Commercially Confidential Information
[14] Five samples will be collected: predose, 0-4, 4-8, 8-12 and 12-24 h post dose
[15] CYP2C8 genotyping screening test is needed at only one time point during screening or baseline. If not done at screening and Day -1 and Day 1 visits are combined, the sample should be collected pre-dose on Day 1.
[16] Commercially Confidential Information
[17] Only one Baseline PET scan will be done during the screening period or at latest at Day -1. The PET scan should always be conducted after all other assessments are done and participant fulfills all other inclusion criteria (PET scan can proceed if a local result for rs6971 genotyping is available, but enrollment cannot occur until the central lab result is available). Baseline PET scan cannot occur on Day 1 if Day -1 and Day 1 visits are combined. If the visits are combined, the PET scan and arterial blood collection should be done in the screening period.
[18] The 2nd PET scan needs to be of sufficient quality allowing analysis for the participant to be considered for the PD analysis.
[19] A 3rd PET scan will be performed either on Day 8 OR Day 14 OR Day 19. A 3rd PET scan will only be performed for cohorts at higher doses than 300mg.
The participants of the 600mg cohort, will receive a PET scan at 10 days after last dose. For the following cohorts it may be decided to perform the 3rd PET scan on the best timing based on the outcomes of the earlier cohorts (either 4, 10 or 15 days post last dose), which will be decided at the dose escalation meetings.
[20] The MRI assessment can be conducted at any time during the screening period once eligibility of the participant is confirmed on all other eligibility assessments (MRI can proceed if a local result is available for rs6971 genotyping is available). The assessment will be performed before the PET scan and can be conducted independently of the screening visit. This assessment will be done during the PET acquisition if a PET/MRI scanner is used. Historical MRIs within the past year may be used, pending central imaging reader approval.
[21] Participant is discharged on this day after assessments unless otherwise determined by the investigator.
[22] Day -1 visit can be combined with Day 1 visit per the discretion of the investigator. If combined, Day -1 assessments not previously done at screening need to be done on Day 1 prior to dose administration.
[23] Day 8 OR Day 14 OR Day 19 will be conducted, but not all three. The visit to be conducted depends on the cohort, and is decided at the dose escalation meeting.
[24] Participants may have the option to complete study activities in conjunction with home nursing during these study days.

[25] To be completed within 3 days prior to dosing.

**Table 8-2 Details for highly repetitive assessments**

Commercially Confidential Information

| Period | Visit Name | Visit Numbers | Days | Time (post-dose) | PK blood collection (BLZ945) |
|---|---|---|---|---|---|
| **Screening** | Screening | 1 | -42 to -2 | - | |
| | Baseline | 20 | -1 | - | |
| **Treatment** | Treatment | 100 | 1 | Pre-dose | X |
| | | | | 0.5h | X |
| | | | | 1h | X |
| | | | | 2h | X |
| | | | | 4h | X |
| | | | | 6h | X |
| | | | | 8h | X |
| | | | | 12h | X[6] |
| | | 110 | 2 | 24 h (Pre-dose) | X |
| | | 120 | 3 | Pre-dose | X |
| | | 130 | 4 | Pre-dose | X |
| | | | | 0.5h | X |
| | | | | 1h | X |
| | | | | 2h | X |
| | | | | 4h | X |
| | | | | 6h | X |
| | | | | 8h | X |
| | | | | 12h | X[6] |

| Period | Visit Name | Visit Numbers | Days | Time (post-dose) | PK blood collection (BLZ945) |
|---|---|---|---|---|---|
| **Follow-up** | Follow-up | 140 | 5<br>+1 | 24h | X |
| | | 150 | 8<br>±2 | 96h | X[3,4] |
| | | 160 | 14<br>±2 | 240h | X[3,4] |
| | | 170 | 19<br>±2 | - | |
| **EOS** | EOS | 1999 | 36<br>±2 | - | |

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X Assessment to be recorded in the clinical database or received electronically from a vendor

1

2 Commercially Confidential Information

3 Sample to be collected at approximately the same time of the day as previously collected BLZ945 pre-dose samples.

4 For the 300 mg 4-day cohort, participants will have Day 14 sample collected. For subsequent cohorts, this sample is only collected at the time point of the 3rd PET scan.

5 Commercially Confidential Information

6 This assessment is optional for participants who choose to have home nursing during the course of this study.

**Table 8-3 Assessment Schedule, 7 Days dosing cohorts**

| Period | Screening | | Treatment | | | | | | | | Follow-up | | | | EOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Name | Screening | Baseline[23] | Treatment[25] | | | | | | | | Follow-up | | | | EOS |
| Visit Numbers[1] | 1 | 20 | 100 | | 110 | 120 | 130 | 145 | 146 | 147 | 150 | 180[24] | 190[24] | 200[24] | 1999 |
| Days | -42 to -2 | -1 | 1 | | 2 | 3 | 4 | 5 | 6 | 7 | 8 +1 | 11 ±2 | 17 ±2 | 22 ±2 | 40 ±2 |
| Time (post-dose) | - | - | - | Pre-dose | - | - | - | - | - | - | - | - | - | - | - |
| Informed consent | X | | | | | | | | | | | | | | |

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| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Inclusion / Exclusion criteria | S | S | | S | | | | | | | | | | | |
| Study completion information | | | | | | | | | | | | | | | X |
| Demography | X | | | | | | | | | | | | | | |
| Detailed Medical History / Current Medical Condition[2] | X | | | | | | | | | | | | | | |
| Hepatitis screen[3] | S | | | | | | | | | | | | | | |
| Alcohol Test and Drug Screen [3] | S | | | | | | | | | | | | | | |
| HIV screen[3] | S | | | | | | | | | | | | | | |
| Quantiferon testing [3] | S | | | | | | | | | | | | | | |
| Covid-19 PCR testing[26] | S | S | | | | | | | | | | | | | |
| Pulse rate | X | | | | | | | | | | X | | | | X |
| Blood Pressure | X | | | | | | | | | | X | | | | X |
| Body Temperature | X | | | | | | | | | | X | | | | X |
| Body Height | X | | | | | | | | | | | | | | |
| Body Weight | X | | | | | | | | | | | | | | |
| Physical examination | S | | | | | | | | | | | | | | S |

| Period | Screening | | Treatment | | | | | | | Follow-up | | | | EOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Name | Screening | Baseline[23] | Treatment[25] | | | | | | | Follow-up | | | | EOS |
| Visit Numbers[1] | 1 | 20 | 100 | 110 | 120 | 130 | 145 | 146 | 147 | 150 | 180[24] | 190[24] | 200[24] | 1999 |
| Days | -42 to -2 | -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 +1 | 11 ±2 | 17 ±2 | 22 ±2 | 40 ±2 |
| Time (post-dose) | - | - | - Pre-dose | - | - | - | - | - | - | - | - | - | - | - |
| Fertility assessment[4] | S | | | | | | | | | | | | | |
| Targeted Neurological Examination[2] | S | | | | | | | | | | | | | S |
| Slow Vital Capacity (SVC)[6] | S | | | | | | | | | | | | | |
| ALS Functional Rating Scale Revised (ALS-FRS-R) | | X | | | | | | | | | | | | X |
| Upper Motor Neuron Burden Scale (UMNB) | X | | | | | | | | | | | | | X |
| Columbia-Suicide Severity Rating Scale (C-SSRS) [7] | X | | | | | | | | | X | X[8] | X[8] | X[8] | X |
| Hematology | X | | | X | X | X | X | X | X | X | X[8] | X[8] | X[8] | X |
| Clinical Chemistry | X | | | X | X | X | X | X | X | X | X[8] | X[8] | X[8] | X |
| Urinalysis | X | | | | | | | | | X | X[8] | X[8] | X[8] | X |
| Thyroid Function Test: T3, T4, TSH[3] | S | | | | | | | | | | | | | |
| Coagulation Panel[3] | X | | | | | | | | | | | | | |
| Electrocardiogram (ECG)[9] | X | | | X | X | X | X | X | X | X | X[8] | X[8] | X[8] | X |
| Pregnancy test[10] | S | S[11] | | | | | | | S | | S[8,11] | S[8,11] | S[8,11] | S |
| Study drug administration | | | X | X | X | X | X | X | X | | | | | |
| Participants domiciled[12,13] | | X | X | X | X | X | X | X | X | X[22] | | | | |
| PK blood collection (BLZ945) | See table below | | | | | | | | | | | | | |

| Period | Screening | | Treatment | | | | | | | Follow-up | | | | EOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Name | Screening | Baseline[23] | Treatment[25] | | | | | | | Follow-up | | | | EOS |
| Visit Numbers[1] | 1 | 20 | 100 | 110 | 120 | 130 | 145 | 146 | 147 | 150 | 180[24] | 190[24] | 200[24] | 1999 |
| Days | -42 to -2 | -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 +1 | 11 ±2 | 17 ±2 | 22 ±2 | 40 ±2 |
| Time (post-dose) | - | - | - Pre-dose | - | - | - | - | - | - | - | - | - | - | - |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PK urine collection (BLZ945) | | | X[15] | | | | | | | X[15] | | | | | |
| Polymorphism rs6971 Genotyping | X | | | | | | | | | | | | | | |
| CYP2C8 Genotyping | X[16] | X[16] | | | | | | | | | | | | | |

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| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PET scan | X[18] | X[18] | | | | | | | | | X[19] | X[20] | X[20] | X[20] | |
| Arterial Blood Collection | X[18] | X[18] | | | | | | | | | X | X[8] | X[8] | X[8] | |
| Brain MRI[21] | X | | | | | | | | | | | | | | |
| Adverse Events | X | | | | | | | | | | | | | | |
| Concomitant medications | X | | | | | | | | | | | | | | |

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Visit structure given for internal programming purpose only
[2] Please refer to the SOM for more details.
[3] Screening test is done in local lab only.
[4] Only for women - medical documentation of fertility; see section Pregnancy and assessments of fertility (in Section 8.4.3).
[5] This footnote has been intentionally deleted in amendment 03 of the protocol.
[6] Historical documentation of up to 3 months old is also acceptable.
[7] The Columbia-Suicide Severity Rating Scale (C-SSRS) also needs to be performed at any unscheduled visit.
[8] To be performed only if the 3rd PET scan is taking place at this time point.
[9] During the study, 12-lead ECGs should be conducted prior to blood collection.
[10] Serum pregnancy test result needs to be available and negative before dosing of the PBR28 tracer for the PET scan and the first BLZ945 dosing.
[11] The serum pregnancy test result is preferred prior to each planned PET scan. Site can perform PET scan if result of urine pregnancy test within 24 hours of PET scan is negative, and local practice allows. [12] Participants may have the option of home nursing during study days 1-7
[13] Percent consumption of meals need to be recorded during the domiciliation period or during the period that the participants are having home nursing visits.
[14] Commercially Confidential Information
[15] Five samples will be collected: predose, 0-4, 4-8, 8-12 and 12-24 h post dose
[16] CYP2C8 genotyping screening test is needed at only one time point during screening or baseline. If not done at screening and Day -1 and Day 1 visits are combined, the sample should be collected pre-dose on Day 1.
[17] Commercially Confidential Information
[18] Only one Baseline PET scan will be done and this during the screening period or at latest at Day -1. The PET scan should always be conducted after all other assessments are done and participant fulfills all other inclusion criteria (PET scan can proceed if a local result for rs6971 genotyping is available, but enrollment cannot occur until the central lab result is available). Only a Baseline PET scan of sufficient quality allowing analysis will be considered for eligibility. Baseline PET scan cannot occur on Day 1 if Day -1 and Day 1 visits are combined. If the visits are combined, the PET scan and arterial blood collection should be done in the screening period.
[19] The 2nd PET scan needs to be of sufficient quality allowing analysis for the participant to be considered for the PD analysis.
[20] A 3rd PET scan will be performed either on Day 8 OR Day 14 OR Day 19. A 3rd PET scan will only be performed for cohorts at higher doses than 300mg. For the following cohorts it may be decided to perform the 3rd PET scan on the best timing based on the outcomes of the earlier cohorts (either 4, 10 or 15 days post last dose), which will be decided at the dose escalation meetings.
[21] The MRI assessment can be conducted at any time during the screening period once eligibility of the participant is confirmed on all other eligibility assessments (MRI can proceed if a local result for rs6971 genotyping is available). The assessment will be performed before the PET scan can be conducted independently of the screening visit. This assessment will be done during the PET acquisition if a PET/MRI scanner is used. Historical MRIs within the past year may be used, pending central imaging reader approval.
[22]Participant is discharged on this day after assessments unless otherwise determined by the investigator
[23] Day -1 visit can be combined with Day 1 visit per the discretion of the investigator. If combined, Day -1 assessments not previously done at screening need to be done on Day 1 prior to dose administration.
[24] Day 11 OR Day 17 OR Day 22 will be conducted, but not all three. The visit to be conducted depends on the cohort, and is decided at the dose escalation meeting.

[25] Participants may have the option to complete study activities in conjunction with home nursing during these study days

[26] To be completed within 3 days prior to dosing

**Table 8-4 Details for highly repetitive assessments**

Commercially Confidential Information

| Period | Visit Name | Visit Numbers | Days | Time (post-dose) | PK blood collection (BLZ945) |
|---|---|---|---|---|---|
| **Screening** | Screening | 1 | -42 to -2 | - | |
| | Baseline | 20 | -1 | - | |
| **Treatment** | Treatment | 100 | 1 | Pre-dose | X |
| | | | | 0.5h | X |
| | | | | 1h | X |
| | | | | 2h | X |
| | | | | 4h | X |
| | | | | 6h | X |
| | | | | 8h | X |
| | | | | 12h | X[6] |
| | | 110 | 2 | 24 h (Pre-dose) | X |
| | | 120 | 3 | Pre-dose | X |
| | | 130 | 4 | - | |
| | | 145 | 5 | - | X |
| | | 146 | 6 | - | |
| | | 147 | 7 | Pre-dose | X |
| | | | | 0.5h | X |
| | | | | 1h | X |
| | | | | 2h | X |
| | | | | 4h | X |
| | | | | 6h | X |
| | | | | 8h | X |
| | | | | 12h | X[6] |

| Period | Visit Name | Visit Numbers | Days | Time (post-dose) | PK blood collection (BLZ945) |
|---|---|---|---|---|---|
| **Follow-up** | Follow-up | 150 | 8<br>+1 | 24h | X |
| | | 180 | 11<br>±1 | 96h | X[3,4] |
| | | 190 | 17<br>±1 | 240h | X[3,4] |
| | | 200 | 22<br>±1 | - | |
| **EOS** | EOS | 1999 | 40<br>±2 | - | |

Commercially Confidential Information

X Assessment to be recorded in the clinical database or received electronically from a vendor

[1]
[2] Commercially Confidential Information

[3] Sample to be collected at approximately the same time of the day as previously collected BLZ945 pre-dose samples.
[4] To be collected at the time point of the 3rd PET scan.

[5] Commercially Confidential Information

[6] This assessment is optional for participants who choose to have home nursing during the course of this study

**Table 8-5 Assessment Schedule Cohort 5**

| Period | Screening | | Treatment | | | | | | | | Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit name | Screening | Baseline | Treatment | | | | | | | EoT 1 | EoS 1 |
| Days | -42 to -1 | -15 to 1 (pre-dose) | 1[13,19] | 4[14,19] | 15[19] ±2 | 29 ±3 | 43[19] ±3 | 57 ±3 | 74 ±3 | 85[20] ±3 | 113[20] ±7 |
| Weeks of treatment | | | HNV Week 0 | HNV Week 0 | HNV Week 2 | Week 4 | HNV Week 6 | Week 8 | Week 10 | Week 12 | Week 16 |
| Informed consent | X | | | | | | | | | | |
| Inclusion / Exclusion criteria | S | S | | | | | | | | | |
| Demography | X | | | | | | | | | | |
| Medical History / Current Conditions[1] | X | | | | | | | | | | |
| ALS history | X | | | | | | | | | | |
| Screening laboratory assessments, Thyroid function[2] | S | | | | | | | | | | |
| Coagulation panel | X | | | | | | | | | | |
| COVID-19 testing | | S[7] | | | | | | | | | |
| Vital signs[3] | X | X | X | X | X | X | X | X | X | X | X |
| Physical Examination | S | | | | | S | | S | | S | S |
| Fertility assessment[4] | S | | | | | | | | | | |
| Targeted Neurological Examination | S | | | | | | | | | | |

| Period | Screening | | Treatment | | | | | | | | Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit name | Screening | Baseline | Treatment | | | | | | | EoT 1 | EoS 1 |
| Days | -42 to -1 | -15 to 1 (pre-dose) | 1[13,19] | 4[14,19] | 15[19] ±2 | 29 ±3 | 43[19] ±3 | 57 ±3 | 74 ±3 | 85[20] ±3 | 113[20] ±7 |
| Weeks of treatment | | | HNV Week 0 | HNV Week 0 | HNV Week 2 | Week 4 | HNV Week 6 | Week 8 | Week 10 | Week 12 | Week 16 |
| (SVC) | | | | | | | | | | | |
| Upper Motor Neuron Burden Scale (UMNB)[12] | X | | | | | | | | | | |
| Columbia-Suicide Severity Rating Scale (C-SSRS)[6] | X | | | | | X | | X | | X | X |
| Clinical chemistry | X | X | X | X | X | X | X | X | X | X | X |
| Hematology | X | X | X | X | X | X | X | X | X | X | X |
| Urinalysis | X | | | | X | X | X | X | X | X | X |
| Electrocardiogram (ECG)[8] | X | X | X | X | | X | | X | | X | X |
| Ventilation | X | | | | | | | | | | |

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| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cardiac echocardiography[10] | X | | | | | | | | | X | |
| Esophagus CT scan[10,11] | | X | | | | | | | | X | |
| Feeding tube placement | X | | | | | | | | | | |
| Pregnancy test[9] | S | | | | | S | | S | | S | S |
| Polymorphism rs6971 Genotyping[12] | X | | | | | | | | | | |
| Randomization | | X[21] | | | | | | | | | |

| Period | Screening | | Treatment | | | | | | | | Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit name | Screening | Baseline | Treatment | | | | | | | EoT 1 | EoS 1 |
| Days | -42 to -1 | -15 to 1 (pre-dose) | 1[13,19] | 4[14,19] | 15[19] ±2 | 29 ±3 | 43[19] ±3 | 57 ±3 | 74 ±3 | 85[20] ±3 | 113[20] ±7 |
| Weeks of treatment | | | HNV Week 0 | HNV Week 0 | HNV Week 2 | Week 4 | HNV Week 6 | Week 8 | Week 10 | Week 12 | Week 16 |
| Study drug dispensing | | X[21] | | | | X | | X | | | |
| Study drug administration | | | Repeated cycles of 4/10 in Arm #1, QW in Arm #2 | | | | | | | | |
| Patient diary | X | | | | | | | | | | |
| Training for study drug administration via feeding tube | | As required | | | | | | | | | |

Commercially Confidential Information

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Study completion information | | | | | | | | | | | X |

| Period | Screening | | Treatment | | | | | | | | Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit name | Screening | Baseline | Treatment | | | | | | | EoT 1 | EoS 1 |
| Days | -42 to -1 | -15 to 1 (pre-dose) | 1[13,19] | 4[14,19] | 15[19] ±2 | 29 ±3 | 43[19] ±3 | 57 ±3 | 74 ±3 | 85[20] ±3 | 113[20] ±7 |
| Weeks of treatment | | | HNV Week 0 | HNV Week 0 | HNV Week 2 | Week 4 | HNV Week 6 | Week 8 | Week 10 | Week 12 | Week 16 |
| Adverse Events | X | | | | | | | | | | |
| Concomitant medications | X | | | | | | | | | | |

HNV: Home Nursing Visits

[S]Assessment to be recorded in the source documentation only.

[1] Please refer to the SOM for more details.
[2] Screening tests are analysed by the local laboratory only. Screening tests consist of hepatitis, HIV, quantiferon or similar test, and drug screen

[3] Vital signs: Pulse rate, Blood Pressure, Body Temperature. In addition: Body Height at Screening and Body Weight at Screening and EoT 1
[4] Only for women - Historical documentation is also acceptable; see section Pregnancy and assessments of fertility (in Section 8.4.3).

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[6] The Columbia-Suicide Severity Rating Scale (C-SSRS) also needs to be performed at any unscheduled visit.
[7] To be completed within 3 days prior to dosing
[8] During the study, triplicate 12-lead ECGs should be conducted, 2 hours post-dose (+/- 2h) during treatment period and prior to blood collection during screening and follow-up periods.
[9] Serum pregnancy tests. CCI serum pregnancy test only at baseline. PET Sub-study: During screening period, the serum pregnancy test result needs to be available and negative before dosing of the PBR28 tracer for the PET scan. If PET scan is performed during screening visit, an additional urine pregnancy test to be performed during baseline visit.

[10] Additional ad hoc in case of moderate or severe AE of facial swelling or unexpected dysphagia, also see footnote #20

[11] These assessments should be performed only after all other eligibility criteria are met. ALS SOC refers to riluzole and/or sodium phenylbutyrate/taurursodiol.

[12] PET sub-study only.
[13] Only applicable for participants on Arm #2, 4 hours post-dose

[14] Only applicable for participants on Arm #1, 4 hours post-dose

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[16] The Baseline PET scan should always be conducted after all other assessments are done and participant fulfills all other inclusion criteria (PET scan can proceed if a local result for rs6971 genotyping is available, but dosing cannot occur until the central lab result is available).

[17] The MRI assessment can be conducted at any time during the screening period once eligibility of the participant is confirmed on all other eligibility assessments (MRI can proceed if a local result is available for rs6971 genotyping is available). The assessment will be performed before the PET scan and can be conducted independently

| Period | Screening | | Treatment | | | | | | | | Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit name | Screening | Baseline | Treatment | | | | | | | EoT 1 | EoS 1 |
| Days | -42 to -1 | -15 to 1 (pre-dose) | 1[13,19] | 4[14,19] | 15[19] ±2 | 29 ±3 | 43[19] ±3 | 57 ±3 | 74 ±3 | 85[20] ±3 | 113[20] ±7 |
| Weeks of treatment | | | HNV Week 0 | HNV Week 0 | HNV Week 2 | Week 4 | HNV Week 6 | Week 8 | Week 10 | Week 12 | Week 16 |

of the screening visit. This assessment will be done during the PET acquisition if a PET/MRI scanner is used. Historical MRIs within the past year may be used, pending central imaging reader approval.

[18] Genetic ICF must be obtained before the optional DNA sampling. This optional sample can be collected anytime on Day 1 or thereafter.

[19] Participants have the option to complete study activities during home visits.

[20] Patients with safety findings at Week 12 (i.e., clinically relevant changes on CT scan or echocardiography, unresolved vasculitis) will perform the Extended safety follow up visit/EoS 1 on Week 24 and cannot continue with the 24 weeks extended treatment.

[21]After eligibility was confirmed

[22]In case of early discontinuation

[23] Additional ad-hoc samples may be required. See Table 16-2

**Table 8-6 Details for highly repetitive assessments in Cohort 5**

| Period | Visit Name | Days | Time (BLZ945 post-dose) | PK blood collection[4] (BLZ945) Arm #1 (4/10) | PK blood collection[4] (ALS SOC) Arm #1 (4/10) | PK blood collection[4] (BLZ945) Arm #2 (QW) |
|---|---|---|---|---|---|---|
| **Treatment** | Treatment | 1[1] | Pre-dose | | | X |
| | | | 1h | | | X |
| | | | 2h | | | X |
| | | | 4h | | | X |
| | | 4[2] | Pre-dose | X | X | |
| | | | 1h | X | X | |
| | | | 2h | X | X | |
| | | | 4h | X | X | |
| | | **74 ±3[5]** | | X | X | X |

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X Assessment to be recorded in the clinical database

[1] Treatment arm #2

[2] Treatment arm #1

[3]The PK sampling time points are defined with respect to the BLZ945 dose administration

[4] Percent consumption of meals need to be recorded on the days when PK samples are collected. Commercially Confidential Information

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**Table 8-7 Assessment schedule for Cohort 5 extended treatment period**

| Period | Follow up | Extended treatment | | | | | | End of the study |
|---|---|---|---|---|---|---|---|---|
| Visit name | EoS 1[2] /Baseline[3] | Extended treatment | | | | | EoT 2 | EoS 2 |
| Days | 113 ±7 | 141 ±3 | 169 ±3 | 197 ±3 | 225 ±3 | 253 ±3 | 281 ±3 | 365, 449, 533, 617 ±7 |
| Weeks of treatment | Week 16 | Week 20 | Week 24 | Week 28 | Week 32 | Week 36 | Week 40 | Week 52, 64, 76, 88 |
| Informed consent | X | | | | | | | |
| Inclusion/Exclusion criteria | X | | | | | | | |
| COVID-19 testing | X | | | | | | | |
| Vital signs | X | X | | X | X | | X | |
| Physical Examination | S | S | | S | S | | S | |
| Commercially Confidential Information | | | | | | | | |
| ALS vital status | X | X | X | X | X | X | X | X[1] |
| Commercially Confidential Information | | | | | | | | |
| Ventilation | X | | | | | | | |
| Feeding tube placement | X | | | | | | | |
| Columbia-Suicide Severity Rating Scale (C-SSRS) | X | X | | X | X | | X | |
| Clinical chemistry | X | X | | X | X | | X | |
| Hematology | X | X | | X | X | | X | |
| Urinalysis | X | X | | X | X | | X | |
| Electrocardiogram (ECG) | X | X | | X | X | | X | |
| Commercially Confidential Information | | | | | | | | |

| Period | Follow up | Extended treatment | | | | | | End of the study |
|---|---|---|---|---|---|---|---|---|
| Visit name | EoS 1[2] /Baseline[3] | Extended treatment | | | | | EoT 2 | EoS 2 |
| Days | 113 ±7 | 141 ±3 | 169 ±3 | 197 ±3 | 225 ±3 | 253 ±3 | 281 ±3 | 365, 449, 533, 617 ±7 |
| Weeks of treatment | Week 16 | Week 20 | Week 24 | Week 28 | Week 32 | Week 36 | Week 40 | Week 52, 64, 76, 88 |
| Commercially Confidential Information | | | | | | | | |
| Cardiac echocardiography | X | | | | | | X | |
| Esophagus CT scan | X | | | | | | X | |
| Serum pregnancy test | S | S | S | S | S | S | S | |
| Study drug dispensing | X | X | X | X | X | X | | |
| Study drug administration | X | | | | | | | |
| Training for study drug administration via feeding tube | As required | | | | | | | |
| Patient diary | X | | | | | | | |
| Commercially Confidential Information | | | | | | | | |
| Concomitant medications | X | | | | | | | |
| Adverse events | X | | | | | | | |
| Study completion information | | | | | | | | X |

[X]Assessment to be recorded in the clinical database

[1]Phone calls

[2] 3rd PET scan for the PET sub-study in addition

[3] Extension Baseline visit may not coincide with Day 113/Week 16 visit for participants who completed the 12 week treatment period under previous protocol amendment versions

[4] Additional ad-hoc samples may be required. See Table 16-2

## 8.1 Screening

### 8.1.1 Eligibility screening

It is permissible to re-screen a participant if she/he fails the initial screening and the reason for failure is anticipated to be transient (e.g., positive COVID-19 test, abnormal laboratory values, temporary conditions e.g., flu symptoms or urinary tract infections).

Re-screening may be allowed under other circumstances, however, each case must be discussed and agreed with the Sponsor on a case-by-case basis. The details of the re-screening process can be found in the SOM.

### 8.1.2 Information to be collected on screening failures

Information on what data must be collected for screening failures and further information on re-screening is outlined in the SOM.

## 8.2 Participant demographics/other baseline characteristics

Participant demographic and baseline characteristic data are to be collected on all participants.

Relevant medical history/current medical condition present before signing the informed consent will be recorded. Investigators will have the discretion to record abnormal test findings on the appropriate CRF whenever, in their judgment, the test abnormality occurred prior to the informed consent signature. Details are outlined in the Site Operations Manual.

Selected laboratory parameters will be assessed to determine patient eligibility. Please refer to Table 8-9.

The Upper Motor Neuron Burden Scale (UMNB) is a scale that measures deep tendon reflexes and pathological reflexes. UMNB scale scores have been found to be positively associated with glial activation as measured by [$^{11}$C]-PBR28 uptake on PET imaging (Zürcher et al 2015, Alshikho et al 2016, Alshikho et al 2018). In Cohorts 1-4, the CCI and the UMNB scale will be collected from all study participants at baseline and at end of study. In Cohort 5, UMNB will be collected at Screening from all participants.

The slow vital capacity (SVC) will be measured during the screening period for participants enrolled in Cohorts 1 to 4, and during the entire study duration in Cohort 5 as per Table 8-5 and extended treatment period as per Table 8-7.

## 8.3 Efficacy

### 8.3.1 Efficacy assessment

Efficacy will be assessed by PET imaging of [$^{11}$C]-PBR28 binding as a measure of the pharmacodynamic effect of BLZ945 on brain microglia.

To avoid unnecessary radiation to the participants, all screening activities except imaging need to be completed prior to PET scan. PET scan can proceed if a local rs6971 genotyping result is available, but enrollment cannot happen until the central lab result is available.

Each participant will have a 3-D structural MRI scan to provide an anatomical image that will help for delineation of the brain regions of interest (ROIs). If a combined PET/MRI scanner is used, which allows simultaneous acquisition of the MRI and PET data, the anatomical MRI scan will be acquired at the beginning of the PET examination.

Refer to Section 3 for more information about PET scan timing, and decision-making processes regarding the timing.

On each day of PET scanning, a cannula will be inserted into the left or right antecubital vein for radioligand administration and another cannula into the radial artery of the contralateral arm for blood sampling.

All participants will undergo brain [$^{11}$C]-PBR28 PET imaging on state-of-the-art, 3D PET scanners. For consistency, the same PET scanner should be used at screening and follow up scans.

The participants will be positioned in the PET scanner. If HRRT PET or PET/CT systems are used, a transmission scan will be acquired to generate the attenuation correction for the emission PET sinograms. If a PET/MRI scanner is used, an MRI scan will be acquired and used for anatomical localization and generation of the attenuation correction maps. After this scan, [$^{11}$C]-PBR28 (approx. 350 MBq) will be injected as a bolus for about 30-60 (depending on the volume) sec via the venous cannula. The dynamic emission scan will be started simultaneously to the radioligand administration. PET examination will have a total duration of approx. 90 minutes. Arterial blood samples will also be collected during the course of the PET scan to determine the metabolite corrected arterial plasma input function that will be used in the quantification of the PET data. Further details on the arterial blood collection will be available in the SOM.

The MRI image for each participant will be co-registered to his PET image and the different ROIs will be defined. Arterial input fraction based compartmental models are considered the gold standard of PET image quantification. and estimation of the volume of distribution (Vt). Vt will be utilized for estimation of [$^{11}$C]-PBR28 binding to TSPO. Analysis of the scan will be centralized. The results of the post-treatment scans will be compared to baseline. Detailed information will be provided in a separate imaging manual.

The relationship between the TSPO binding and BLZ945 exposure will be calculated graphically.

### 8.3.2 Appropriateness of efficacy assessments

This study will use [$^{11}$C]PBR28 imaging to provide evidence for microglia reduction in ALS participant on BLZ945 treatment. PET is a noninvasive molecular imaging technique that enables quantification of neuropathological markers and pharmacodynamic properties of new drug candidates. In vivo functional imaging of activated microglia has been widely explored by PET. TSPO is minimally expressed in resting (homeostatic) microglia in the healthy brain but its expression is upregulated during the microglial activation process in several neurodegenerative and neuroinflammatory diseases including ALS. TSPO is widely recognized as a reference molecular biomarker for PET imaging of activated microglia. The TSPO PET tracer [$^{11}$C-PBR28] has been used in different clinical trials to image microglial activation in ALS participants (Zürcher et al 2015; Alshikho et al 2018; Albrecht et al 2018).

## 8.4 Safety and tolerability

Safety and tolerability assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section (Section 10.1).

The methods, assessment, specification, and recording for each assessment will be detailed in the SOM.

**Table 8-8 Assessments and specifications**

| Assessment | Specification |
|---|---|
| Physical Examination | The examination of general appearance, skin (e.g., purpura; see guidance in Section 16.3), neck (including thyroid), head, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological (e.g. new onset of paresthesia or dysesthesia). If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed. |
| Targeted Neurological Examination | Assessment of muscle strength, deep tendon reflexes, and the presence of pathologic reflexes (Hoffman, Babinski, and jaw jerk). UMNB is scored based on results from the neurological examination. |
| Medical History | Detailed medical history should be collected. |
| Vital signs | Vital signs include body temperature, blood pressure and pulse measurements. |
| Height and weight | Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes). |

### 8.4.1 Laboratory evaluations

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Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

All laboratory parameters assessed for safety purposes will be evaluated locally while primarily the liver enzymes and related lab tests will also be assessed centrally. Refer to Table 8-9 for a summary of the parameters and where these are to be evaluated.

More frequent evaluations may be performed at the investigator's discretion if medically indicated; results should be recorded as unscheduled laboratory assessments.

Novartis will be provided with a copy of the laboratory certification and tabulation of the normal ranges for each parameter required. In addition, if at any time a participant has laboratory parameters obtained from a different outside laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges for that laboratory.

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion).

Safety samples that can be collected remotely during home nursing visits will be collected and analyzed in line with the study laboratory manual. If participants cannot visit the site for safety laboratory assessments conducted through central laboratories, local laboratory collection may be used during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits.

For those laboratory adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

**Table 8-9 Laboratory evaluations**

| Test Category* | Test Name | Central or Local laboratory |
|---|---|---|
| Hematology | Cohorts 1-5: Hematocrit, Hemoglobin, MCV, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)<br>Cohort 5: Erythrocyte sedimentation rate | Local |
| Chemistry | Cohorts 1-5: Albumin, Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Glucose, Total Protein | Local |
| Chemistry | Cohorts 1-5: Amylase, Lipase, Alkaline phosphatase, ALT, AST, Creatine kinase (CK), CK-MB, Troponin, GGT, Total Bilirubin (also measure direct and indirect bilirubin if total bilirubin is > grade 1, i.e., increased above 1.5 x ULN)<br>Cohort 5: C-reactive protein | Local and Central*,** |
| Screening | Cohorts 1-5: Tuberculosis, Hepatitis B and C, HIV (ELISA and Western Blot), Alcohol test (Cohorts 1-4) and drug screen, Direct Bilirubin, COVID-19 test | Local |
| Urinalysis | Cohorts 1-5: Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells)<br>Cohorts 1-5: Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) | Local |
| Coagulation | Cohorts 1-5: Prothrombin time (PT), International normalized ratio ([INR]), Partial thromboplastin time (PTT) or Activated | Local |

| Test Category* | Test Name | Central or Local laboratory |
|---|---|---|
| | partial thromboplastin time (APTT) | |
| Thyroid | Cohorts 1-5: T3 [free], T4 [free], TSH | Local |
| Pregnancy Test | Cohorts 1-4: Serum / Urine pregnancy test only for women of child-bearing potential<br>Cohort 5: Serum pregnancy test only for women of child-bearing potential | Local |
| Genotyping rs6971 polymorphism | Cohorts 1-5: Genotyping rs6971 polymorphism | Central* or Local*** |
| Genotyping CYP2C8 | Cohorts 1-5: Genotyping CYP2C8 | Central* |



* Details will be provided in the laboratory manual.
** For eligibility, the local laboratory results will be used and for the dose escalation reviews, the central laboratory results will be used.
***If CLIA certification available

### 8.4.2 Electrocardiogram (ECG)

Full details of all procedures relating to the ECG collection and reporting are contained in the Site Operations Manual.

A standard 12-lead ECG will be performed as per the assessment schedule in Table 8-1, Table 8-5 and Table 8-7. Blood samples scheduled at the same clock time point should be taken **after** the ECGs are completed. The ECGs must be performed in triplicate in supine position.

PR interval, QRS duration, heart rate, RR interval, QT interval, QTcF will be recorded.

The Fridericia QT correction formula (QTcF) must be used for clinical decisions.

As applicable, QTcF may be calculated in-house. Unless auto-calculated by the ECG machine, the investigator must calculate QTcF at the Screening and/or Baseline visit(s) (as applicable) to assess eligibility. Since the ECGs are done in triplicate, the average of the three QTcF values should be used to determine eligibility.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG. Each ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, and date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the Medical History eCRF. Clinically significant findings must be discussed with Novartis prior to enrolling the participant in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF. All eligibility and participant management decisions should be made based on the local reading of the ECG. An ECG may be replaced if, in the opinion of the qualified physician, the tracing is not representative of the participant's baseline.

See the SOM for additional details.

### 8.4.3 Pregnancy and assessments of fertility

A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study drug via seminal fluid to their partner. In addition, male participants should not donate sperm for the period from dosing start till EOS visit.

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

Any woman of child bearing potential with a positive pregnancy test will be excluded from the study.

Refer to Table 8-1, Table 8-3, Table 8-5 and Table 8-7 for more guidance about pregnancy testing timing and accepted test methods.

#### Assessments of fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline.

### 8.4.4 Cardiac imaging – echocardiogram

Echocardiograms will be performed at the visits defined in the assessment schedule (Table 8-5 and Table 8-7). A subset of a standard echocardiographic two-dimensional and doppler examination will be performed. The images will be sent to a central reading vendor for independent review and analysis. Echocardiographic assessments may include but are not limited to:

- Left ventricular ejection fraction (LVEF)
- Left ventricular diastolic/systolic volumes
- Left ventricular dimensions
- Cardiac valve thickness, stenosis, and regurgitation

Please refer to Section 9.1.1 for end of treatment echocardiogram in case of premature discontinuation and to Section 10.2.4 for monitoring in case of abnormalities at EoT 1 visit (Week 12).

### 8.4.5 Esophageal computed tomography (CT) scan

Esophageal CT-scans will be performed at the visits defined in the assessment schedule to evaluate esophageal wall thickness (EWT).

Esophagus CT scans will be acquired in the supine position. In all participants, the baseline and follow-up CT scans should be performed where possible on the same scanner. The EWT

will be evaluated at three anatomic landmarks: at the level of the carina, a few centimeters above the gastroesophageal junction, and some centimeters below the cricopharyngeus to measure the upper, mid and lower thoracic esophagus with consistency. The images will be sent to a central reading vendor for independent review and analysis. Protocol specific requirements of the CT and machine settings will be provided to the sites as part of a separate Imaging Manual.

Please refer to Section 9.1.1 for end of treatment CT scan in case of premature discontinuation.

In the event of the report of unexpected worsening of swallowing, or if onset of facial or periorbital swelling of moderate or severe intensity is detected, an ad hoc CT scan of the chest must be performed to evaluate for possible esophageal thickening within 2 weeks of the event. Please refer to Section 10.2.4 for monitoring in case of abnormalities at EoT 1 visit (Week 12).

Note: The coded medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers.

### 8.4.6 Markers of inflammation

In the absence of clinically validated markers for the assessment of BLZ945-induced vascular inflammation, markers of general inflammation (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)) will be measured at the times indicated in the assessment schedule.

Additional diagnostic work will be performed, in the event of signs and symptoms of vascular inflammation or in the event of elevations in ESR and CRP (refer to Table 16-6 for ESR and CRP values triggering additional evaluation).

Please refer to Section 10.2.3 for monitoring of vasculitis.

### 8.4.7 Appropriateness of safety measurements

The selected safety assessments will take advantage of the clinical expertise of the investigators who are familiar with the standard care of ALS patients. A full battery of standard clinical laboratory measurements will be collected for safety purposes. In addition, effects of ECM accumulation on target organs (i.e., heart and esophagus) will be assessed via echocardiography and CT scan. Echocardiography is the most commonly used imaging technique to monitor cardiac valve and cardiac function (Lang et al 2015, Vahanian et al 2022) and CT scan is the most commonly used method for assessing esophageal wall thickness (Reinig et al 1983, Berkovich et al 2000). Physical examination and laboratory measurements, such as markers of general inflammation (i.e., ESR and CRP), complete blood count, liver and renal function tests (creatinine, BUN, electrolytes and urinalysis), cardiac enzymes, will be analyzed for assessing potential cases of vasculitis.

### 8.4.8 COVID-19 contingency plan

The sponsor recommends that subjects in the study are screened for symptomatic or asymptomatic carriage of SARS-CoV-2 at any time during the entire study duration as deemed necessary by the investigator taking in consideration the study site specific procedures and/or local and national regulatory requirements or guidelines.

Moreover, as part of the clinical study procedures, participants will be closely monitored for signs and symptoms of COVID-19 during the entire study duration.

Any subject that, in the opinion of the investigator, presents COVID-19-related symptoms and/or has a positive SARS-CoV-2 viral test, will be assessed on a case by case basis by the investigator (after consultation with Novartis, as applicable) to determine if the enrollment or further participation in the study is impacted.

## 8.5 Additional assessments

### 8.5.1 Pharmacokinetics

Urine (Cohorts 1-4), plasma (Cohorts 1-5) CCI PK samples will be collected at the visits defined in the assessment schedule. Follow instructions outlined in the Site Operations Manual regarding sample collection, numbering, processing, and shipment. See the potential use of residual samples for more information in Section 8.5.2.2.

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data.

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The details of the assays will be documented in the Bioanalytical Data Report.

Plasma PK samples will be obtained and evaluated in all participants at all dose levels.

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For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol.

For Cohorts 1-4: The following pharmacokinetic parameters will be determined for BLZ945 using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 8.0 or higher):

**Table 8-10 Non-compartmental pharmacokinetic parameters of BLZ945**

| **Plasma** | |
|---|---|
| AUClast | The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1) |
| AUCinf | The AUC from time zero to infinity (mass x time x volume-1) |
| AUC0-24h | The AUC calculated to the end of a dosing interval (tau) (amount x time x volume-1) |
| Cmax | The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1) |

| | |
|---|---|
| **Plasma** | |
| Tmax | The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time) |
| Lambda_z | Smallest (slowest) disposition (hybrid) rate constant (time-1) may also be used for terminal elimination rate constant (time-1) |
| T1/2 | The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives |
| CL/F | The total body clearance of drug from the plasma (volume x time-1) |
| Vz/F | The apparent volume of distribution during terminal phase (associated with λz) (volume) |
| Racc | Accumulation Ratio = Cmax (multiple Dose)/Cmax (single dose) and AUC0-24h (multiple Dose)/AUC0-24h (single dose) |
| Urine | |
| Ae(0-t) | Amount of drug excreted into the urine from time zero to time 't' [mass units] |
| CLR | The renal clearance of drug [volume x time-1] |

For Cohort 5: selected PK parameters of BLZ945, CCI in plasma (Cmax, Tmax, AUClast, Tlast) on Day 1 (Arm 2) and Day 4 (Arm 1) will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 8.0 or higher), as feasible. Commercially Confidential Information

The linear trapezoidal rule will be used for AUC calculation. In cases where the percent extrapolated AUC is greater than 20%, AUCinf values will be indicated as missing values and only AUClast will be reported. Regression analysis of the terminal plasma elimination phase for the determination of T1/2 will include at least 3 data points after Cmax. If the adjusted $R^2$ value of the regression analysis of the terminal phase will be less than 0.75, no values will be reported for T1/2, AUCinf, and CL/F.

BLZ945 renal clearance (CLR) will be estimated from the ratio of the amount of unchanged drug excreted in urine (Ae 0-t) to the corresponding AUC in plasma.

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In Cohort 5: Commercially Confidential Information plasma PK samples will be collected together with BLZ945 at the visits defined in the assessment schedule. The pre-dose PK sample may also be used as a reference of Commercially Confidential Information prior to BLZ945 treatment. If participants experience an SAE or an AE of liver enzyme elevations leading to discontinuation of study treatment, an unscheduled PK blood sample of BLZ945 Commercially Confidential Information should be taken as soon as possible. The date of time of the last dose and the time of PK blood draw must be recorded.

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# 9 Study discontinuation and completion

## 9.1 Discontinuation and completion

### 9.1.1 Study treatment discontinuation and study discontinuation

Discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in Section 6.2.2.
- Any situation in which study participation might result in a safety risk to the participant
- Any laboratory abnormalities that in the judgment of the investigator, prevents the participant from continuing participation in the study
- Severe hypersensitivity reaction occurs, including any of the following: anaphylaxis, fever, chills, urticaria, dyspnea, headache, myalgia, hypotension.
- QTcF on ECG ≥501 ms or a >60 ms change from baseline.
- Development of symptomatic conduction abnormalities requiring urgent intervention.
- Development of symptomatic cardiac arrhythmia requiring urgent intervention.
- For liver events, please see Section 10.2.1 and consult the Hepatotoxicity Clinical Safety Standard Guideline. For renal events, please see Section 10.2.2.
- If a liver or renal event occurs, follow guidelines outlined in Section 16.1 and Section 16.2.
- Unexpected worsening of swallowing associated to abnormal thickening of the oesophagus on ad hoc CT scan.
- Increased thickness of cardiac valve on echocardiography accompanied by clinically meaningful change in valve function (regurgitation or stenosis) or cardiac function (LVEF).
- In case of confirmed vasculitis. For identification of potential cases of vasculitis and their follow-up, follow guidelines outlined in Section 16.3.

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's premature discontinuation of study treatment and record this information.

#### 9.1.1.1 Premature discontinuation of study treatment in Cohort 5

In case of premature discontinuation of study treatment, participants will perform the assessments planned at EoT 1 visit as close as possible to the last dose. In addition to the assessments scheduled at the EoT 1 visit (see Table 8-5), the procedures be performed are listed in Table 9-1.

**Table 9-1 Additional procedures at EoT 1 in case of premature discontinuation of treatment**

| | Discontinuation before Week 4 | Discontinuation between Week 4 and Week 8 | Discontinuation between Week 8 and Week 10 | Timing from last dose |
|---|---|---|---|---|
| LP and blood PK sample or PET | no | no | yes | within 6 days (+/- 1) day |
| CT-scan, echocardiogram | no | yes | yes | within 2 weeks (and at EoS 1) |

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.1.2 Withdrawal of Informed Consent). **Where possible, they should return for the assessments indicated** in the Assessment Schedule as soon as possible. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section (Section 9.1.3).

This contact should preferably be done according to the study visit schedule. If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

In case of premature treatment discontinuation prior to Week 40 in the extended treatment period, participants will perform the assessments from the Week 40 visit as close as possible to the last dose (ideally within 2 weeks). Study site should nevertheless continue with the quarterly contacts over 1 year to collect the vitality status.

#### 9.1.1.2 Replacement policy

Participants will not be replaced on study in the first four cohorts. However, if a participant is considered as non-evaluable for the dose escalation decision, enrollment of a new participant to the current cohort will be considered until at least the minimum number (3) of evaluable participants is achieved within the cohort. If the evaluation of the second PET scan is not possible then the participant may be discontinued and enrollment of a new participant into the current cohort may be considered until at least the minimum number of evaluable participants is achieved within the cohort.

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### 9.1.2 Withdrawal of informed consent

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a participant:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the participant's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a participant's samples until the time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

### 9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

### 9.1.4 Study stopping rules

The study may resume following the safety review, if the Investigator and Sponsor agree it is safe to proceed.

#### 9.1.4.1 Cohort 1-4 stopping rules:

Following dosing for each cohort, dosing of the next cohort will be paused until the Investigator and Sponsor's Medical Monitor discuss the safety and tolerability data from that cohort. Drug administration of subsequent cohorts will only be triggered if an adequate safety and tolerability profile has been confirmed through 10 days after the last treatment from the preceding cohort. A cohort will be stopped if two or more study participants experience dose limiting toxicities (DLTs) as described in Table 9-2 below. No further dosing / dose escalation decisions will be taken pending a full safety review.

Enrollment will be placed on hold and a safety review undertaken if any of the following occurs cumulatively across Cohorts 1-4:

- One study drug related SAE
- Two participants experience SAEs related to dose limiting toxicities, regardless of suspected relatedness to drug
- At least 2 or more participants experience a similar AE which was assessed as severe in intensity (≥CTCAE grade 3), and are considered as potentially related to the study drug;

The Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the study on hold.

A DLT is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs by study day 14 (or day 17 for 7-day dosing).

The DLTs will be assessed according to the standardized grading scale, the NCI (National Cancer Institute) CTCAE version 5. For the purpose of dose- and dosing schedule modification decisions, DLTs will be considered and included in the BLRM.

The investigator must notify the Sponsor immediately of any unexpected CTCAE grade ≥ 3 adverse events or laboratory abnormalities. Prior to enrolling participants into a higher dose level or prior to extending the dosing period, CTCAE grade ≥ 2 adverse events will be reviewed for all participants at the current dose level.

- Following the occurrence of an AE by day 14 (or day 17 for 7-day dosing) for Cohorts 1-4, the observation period to determine whether an AE is considered to be a DLT is through the end of study visit, or longer if deemed necessary by the site investigator or Sponsor.

**Table 9-2 Adverse events that will be considered DLTs Cohorts 1-4**

- ≥ CTCAE grade 3 neutropenia
- ≥ CTCAE grade 3 thrombocytopenia
- ≥ CTCAE grade 3 serum creatinine
- Serum creatinine 2 x ULN for > 7 consecutive days
- Total bilirubin 2 x ULN for > 7 consecutive days
- Total bilirubin 2 x ULN and CTCAE grade 2 AST or ALT
- ≥ CTCAE grade 3 total bilirubin
- ≥ CTCAE grade 3 AST or ALT, unless it resolves to ≤ grade 1 within 7 days
- ≥ CTCAE grade 3 cardiac events
- ≥CTCAE grade 3 ECG QT corrected interval prolongation
- ≥CTCAE grade 3 ECG cardiac conduction disorder
- ≥ CTCAE grade 3 rash
- Other clinically significant toxicities, including a single event or multiple occurrences of the same event that lead to a dosing delay of > 7 days

### 9.1.5 Cohort 5 stopping rules for one treatment arm:

Enrollment in a treatment arm will be placed on hold and a safety review undertaken if any of the following occurs in that specific treatment arm of Cohort 5:

- Two out of the first 6 participants experience SAEs suspected to be related to study drug, or 4 participants overall experience SAEs suspected to be related to the study drug in each treatment arm.
- The Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the study on hold.

Enrollment in that treatment arm may resume following the safety review, if the Sponsor, the DMC, and investigators judge it safe to proceed. In case of safety and/or tolerability concerns resulting from the safety review, a dose reduction in one or both treatment arms may be considered by the Sponsor in consultation with the DMC to resume enrollment.

A treatment arm may be terminated for safety reasons and all ongoing participants switched to the other arm. The study will continue with a single arm design to achieve the target overall sample size.

### 9.1.6 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

## 9.2 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision. Each participant will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

# 10 Safety monitoring and reporting

Safety and adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

## 10.1 Adverse events (AEs), serious adverse events (SAEs), and other safety reporting

### 10.1.1 Definition and recording of adverse events

#### Definition of AEs

An adverse event (AE) is any untoward medical occurrence (e.g., any occurrence of unfavorable and unintended sign(s), symptom(s) or medical condition, including abnormal laboratory findings, or worsening of any pre-existing sign(s), symptom(s) or medical condition) in a participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of any treatment used in this study. This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values considered to be non-typical in participant with the underlying disease.

#### Collecting and assessing AEs

The occurrence of AEs must be sought by non-directive questioning of the participant at each visit during the study. AEs also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments (patient diaries, C-SSRS).

The investigator will attempt to establish a diagnosis of the event (including lab abnormalities that constitute AEs) based on signs, symptoms, and/or other clinical information.

Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE.

For each AE, the investigator must assess:

1. The Common Terminology Criteria for Adverse Events (CTCAE) version.
2. The causality

The investigator is obligated to assess the relationship between any treatment used in the study (study treatment, AxMP(s)) and each occurrence of each AE. The investigator will use clinical judgment to determine the relationship. A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

### Handling of AEs

All adverse events must be treated appropriately. More information about how to manage AEs can be found in the IB. Information about adverse drug reactions can also be found in product information for marketed products.

Once an AE is detected, the Investigator must pro-actively followed up the participant, until resolution of the AE, or until it is judged to be not recovered/not resolved (e.g., continuing at the end of the study), or until stabilization, or until the participant is lost to follow-up. Any change in severity or suspected relationship to study treatment must be assessed at each visit (or more frequently, if necessary).

### Timeframe of recording of AEs

AE recording for each participant should be continued for at least 30 days following the last dose of study treatment.

### Reporting of AEs related to AxMP(s)

All AEs related to authorized auxiliary medicinal product used in this study must be reported to Novartis.

In assessing causality, the investigators will use the points above.

If a suspicion that medical occurrence could be related to study treatment (and/or interaction with study treatment) cannot be ruled out, the reporting rules for study treatment apply.

### 10.1.2 Definition and recording of serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a medical occurrence in which the participant was at risk of death at the time of the reaction; it does not refer to a medical occurrence that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect, fetal death or a congenital abnormality or birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the participant's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All new malignant neoplasms and confirmed cases of vasculitis will be assessed as serious under "medically significant" even if other seriousness criteria are not met.

### 10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the last study visit must be reported to Novartis/safety immediately, without undue delay, but under no circumstances later than

within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. All applicable sections of the form must be completed in order to provide a clinically thorough report.

The investigator must review and provide an assessment of causality for each SAE. There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Novartis. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to Novartis. The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the Investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail).

Any SAEs experienced after the 30-day period should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

### Reporting of SAEs related to AxMP(s)

AxMP safety reporting requirements will only apply once the trial has been transitioned under EU Clinical Trial Regulation 536/2014. Once this is completed, all SAEs related to any AxMP (whether authorized or not) used in this study must be reported to Novartis within 24 hours of the site becoming aware of it. In assessing causality, the investigators will use the points above. If a suspicion that the medical occurrence could be related to study treatment (or and interaction with study treatment) cannot be ruled out, the reporting rules for study treatment apply.

### SAE Reporting via an Electronic Data Collection Tool

The primary mechanism for reporting an SAE to Novartis will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or by telephone.

### Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

If an SAE is not previously documented in the IB or product information for marketed products and is thought to be related to any study treatment, Novartis may urgently require further information from the investigator for HA reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment. SUSARs will be reported to the competent authorities and relevant ethics committees in accordance with national regulatory requirements in participating countries, including EU Clinical Trial Regulation 536/2014.

## 10.1.4 Pregnancy reporting

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until 14 days after the last dose.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- Any post study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported Novartis as described in Section 10.1.3. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

### Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the Investigator to Novartis. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

If a female partner of a male trial participant who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

### 10.1.5 Reporting of study treatment errors including misuse/abuse

Study treatment errors are unintentional errors in the prescribing, dispensing, and administration of study treatment.

Study treatment misuse refers to situations where the study treatment is intentionally and inappropriately used not in accordance with the protocol.

Study treatment abuse corresponds to the persistent or sporadic, intentional excessive use of a study treatment, which is accompanied by harmful physical or psychological effects.

Once the trial has transitioned under EU Clinical Trial Regulation 536/2014, study treatment errors and uses outside of what is foreseen in the protocol, including misuse or abuse, must be reported on the AE (or SAE, if the event meets the definition of an SAE) CRF.

## 10.2 Additional Safety Monitoring

### 10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed. Once a participant is exposed to study treatment, every liver event should be followed up by the investigator or designated personnel at the trial site, as summarized in Section 16.1.

### 10.2.2 Renal safety monitoring

Abnormal renal event findings must be confirmed within 24-48 hours after the first assessment.

Once a participant is exposed to the study treatment, renal laboratory alerts or renal safety events should be monitored and followed up by the investigator or designated trial staff as summarized in Section 16.2, Table 16-4.

Refer to the Site Operations Manual for additional details.

### 10.2.3 Vasculitis safety monitoring

Vasculitis includes a group of disorders characterized by non-specific systemic manifestations resulting from release of chemical mediators from inflamed blood vessels (e.g., fever, weight loss, arthralgia, and myalgia) and more specific manifestations resulting from involvement of various organ systems.

A list of clinical manifestations of vasculitis is provided in Section 16.3, Table 16-6.

Safety monitoring for vascular inflammation will include physical examination at every post-treatment visit (see Table 8-5 and Table 8-7) by the investigator or qualified delegate (including assessment of skin manifestations such as purpura and neurological manifestations such as paresthesia and dysesthesia), assessment of markers of general inflammation (i.e., ESR and CRP), electrocardiogram, and urinalysis in addition to assessment of laboratory parameters such as creatinine, electrolytes, and BUN for assessment of renal involvement.

Participants will be instructed to contact the investigator immediately in case of development of signs and symptoms potentially suggestive of vasculitis.

In the event of signs and symptoms of vascular inflammation or in the event of elevations in ESR and/or CRP (refer to Table 16-7 for ESR and CRP values triggering additional evaluation), further diagnostic work should be performed to identify the primary reason for such increase (e.g., other inflammatory conditions such as bacterial infections). Detailed guidance for the identification and follow-up of potential cases of vasculitis is provided in Section 16.3.

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If a diagnosis of BLZ945-induced vasculitis is made, BLZ945 should be discontinued and a SAE be recorded as a medically significant event (Section 10.1.3) with information captured from clinical management of the case as specified in Appendix 3.

### 10.2.4 Monitoring for ECM accumulation

Signs or symptoms of ECM accumulation may include:

- Macroscopic signs including eyelid / orbital / periorbital swelling
- Cardiac function alterations resulting for example in worsening of dyspnea, chest pain, fatigue, syncope
- Worsening of dysphagia

Assessment of potential effects of BLZ945 on ECM accumulation in the heart (including heart valves) and esophagus will be performed by echocardiography and CT scan at baseline and week 12.

In the event of the report of unexpected worsening of swallowing, or in the event that the onset of facial or periorbital swelling of moderate or severe intensity is detected, an ad hoc CT scan of the chest must be performed to evaluate for possible clinically relevant changes in esophageal thickening within 2 weeks of the event.

In case of clinically relevant changes in esophageal thickness (>3mm increase in mean wall thickness compared to the baseline measurement) detected at week 12, the study participant should be followed for an additional 12 weeks off treatment. At the end of the additional follow-up period, a CT scan will be performed to evaluate the esophageal thickness.

In case of abnormal cardiac valves thickening and/or clinically relevant cardiac valve / cardiac function (stenosis, regurgitation, LVEF) abnormalities detected at week 12, the study participant should be followed for an additional 12 weeks off treatment. At the end of the

additional follow-up period, an echocardiogram should be performed to evaluate the status of the previously identified abnormality.

### 10.2.5 Prospective suicidality assessment

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire that prospectively assesses suicidal ideation and suicidal behavior. The C-SSRS must be administered at the visits indicated in Table 8-1, Table 8-3,Table 8-5 and Table 8-7, as well as at any unscheduled visit.

The C-SSRS, which uses a semi-structured interview to probe participant responses, will be administered by an individual who has received training and certification in its administration. At the first study visit, the "baseline/screening" version of the C-SSRS will be administered. This version assesses suicidal ideation and suicidal behavior during the participant's lifetime and during a predefined period. At subsequent visits, the "since last visit" version will be administered.

If, at any time after screening and/or baseline, the score is "yes" on item 4 or item 5 of the suicidal ideation section of the C-SSRS or "yes" on any item of the suicidal behavior section, the participant must be referred to a mental health care professional for further assessment and/or treatment. The decision on whether the study treatment should be discontinued is to be taken by the investigator in consultation with the mental health professional to whom the participant is referred.

In addition, all life-threatening events must be reported as SAEs. For example, if a participant answers "yes" to one of the questions in the suicidal behavior section, an SAE must be reported if the event was life-threatening. All events of "Non-Suicidal Self-Injurious Behavior" (question also included in the suicidal behavior section) should be reported as AEs and assigned the appropriate severity grade.

# 11 Data Collection and Database management

## 11.1 Data collection

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

## 11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

## 11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/delegated CRO representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/delegated CRO/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

## 11.4 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will review individual and aggregated data from Cohort 5 on a regular basis for safety oversight along with any new information emerging from preclinical toxicity studies. DMC will review all safety and tolerability assessments, including ECGs, laboratory tests, vital signs, adverse events, suicidality, esophageal CT-scans and echocardiogram abnormalities. Commercially Confidential Information

Disposition of participants will include the duration of exposure in Cohort 5 over the 40 weeks of extended treatment and, if applicable, the reason for early treatment discontinuation. DMC may recommend discontinuing treatment in an individual participant, one of the treatment arms or the whole Cohort 5 (see Section 9.1.4).

# 12 Data analysis and statistical methods

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

All primary, secondary CCI endpoints listed below will be analyzed using the same statistical methodology for all cohorts unless explicitly detailed for Cohort 5.

For Cohort 5, participants will be analyzed by the starting dose and regimen (800mg 4/10, 800mg QW, 600mg 4/10 and 400mg QW) to account for the dose reductions implemented in protocol amendment v07. Participants may be pooled across starting doses and regimens as applicable to assess the primary PET objective, Commercially Confidential Information

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For the Cohort 5 secondary CCI endpoints assessing changes from baseline to Week 40, the change from baseline to be summarized primarily refers to the change from the baseline prior to BLZ945 drug administration of the core period. Additional summaries for change from start of extended treatment (Week 16) will also be included as applicable.

## 12.1 Analysis sets

For all analysis sets, which is identical to the safety analysis set, participants will be analyzed according to the study treatment(s) received.

The full analysis set will include all participants that received any study drug.

The PK analysis set will include all participants with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received any study drug, and had no protocol deviations that impact on PK data.

The PD analysis set will include all participants with available PD data and no protocol deviations with relevant impact on PD data.

## 12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data will be summarized descriptively by dose cohort for each dosing cohort.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. Differences from baseline of continuous variables will be presented in the same way.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, and by dose cohort.

## 12.3 Treatments

The duration of exposure in time to BLZ945 will be summarized by means of descriptive statistics using the safety set. Numbers of participants exposed to the different daily doses of BLZ945 will be tabulated.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by dose cohort.

## 12.4 Analysis of the primary endpoint(s)

### Cohorts 1- 4

The fraction of brain microglia reduction following four oral doses of BLZ945 will be analyzed by an Emax model with dose as the independent variable and reduction fraction as the dependent variable. Allometric scaling of a mouse PK/PD model makes it credible that 4 doses at 600 mg for 4 days will lead to a 50% reduction in microglia 18 days past the 4th dose. The same model points to a Hill constant between 1 and 3.3. It hence seems reasonable to analyze all available microglia reduction data at the 5 day time point by a sigmoidal Hill constant model with prior distributions on the EC50 of 600 mg and Hill constant centered at 2. Such a model assumes that the microglia reduction after 4 doses is independently normally distributed among participants with a mean which can be expressed by a two-parameter Emax function. If the microglia depletion fraction at concentration c is denoted Y(c), then the model assumes that

$Y(c) = c^h / (c^h + D^h) + \text{error}$

Here, D and h are the two unknown parameters, the concentration giving a 50% response and the Hill constant.

For the purposes of this study, brain [$^{11}$C]-PBR28 binding reduction of 20% or more has been chosen as sufficient evidence of target engagement to enable further development.

### Cohort 5

Descriptive statistics will be provided by treatment and visit for the cohort 5 for efficacy and safety endpoints. No formal statistical comparison will be carried out between the two treatment arms. For continuous measures, such as percent change from baseline to week 12 in Vt measured via PET scan, esophagus wall thickness change from baseline to week 12 and LVEF change from baseline to week 12, the mean, SD and 95% CI will be provided by treatment arm. For measures such as cardiac valve function (stenosis and regurgitation based on echocardiography) and cardiac valve thickness, the number and frequency of participants

with any worsening between baseline and Week 12 will be presented by treatment arm, as well as the 95% CI for the rate based on the Wilson method. Number and percentages of participants with AEs of ECM accumulation will be summarized by treatment arm.

### 12.4.1 Definition of primary endpoint(s)

#### Cohorts 1-4

The percent change in Vt of the first scan 24 hours after last BLZ945 treatment relative to baseline will be considered as primary endpoint.

#### Cohort 5

The percent change from baseline to Week 12 in Vt measured via PET scan.

The changes from baseline to Week 12 in: esophagus wall thickness (mm), and LVEF (%).

Any worsening from baseline to Week 12 in cardiac valve thickness and cardiac valve function (stenosis and regurgitation).

Adverse events of ECM accumulation during the 12 weeks of treatment.

### 12.4.2 Statistical model, hypothesis, and method of analysis

Cohorts 1, 2, 3 and 4 will receive 4 daily doses of BLZ945, after which the decrease in microglia level will be assessed. Cohort 1 will be dosed at a low dose, and barring any safety concerns while cohorts 2 and 3 will be dosed at increasing dose levels. After four cohorts of 4 participants have been dosed, the sigmoidal model described in Section 12.4 will be fitted to data. That is, a nonlinear regression model of the form

$$Y(c)=c^h /(c^h+D^h)+e$$

will be fitted to the microglia depletion ratio (ratio to baseline) where c denotes the dose level, D is the ED-50 dose, and h is the Hill constant model.

When data from the first 12 participants are available from the 4 day dosing cohorts, the ED-50 and Hill constant parameters will be estimated. The remaining two 4 day dosing cohorts will be allocated to doses in the unexplored part of the dose-response curve; that is, between dose cohorts 1 and 2, and dose cohorts 2 and 3, unless it clear that adding extra design points here will not lead to a more accurate characterization of the dose-response relationship. This is, the predictive variability in the ED-50 estimate available from adding 8 participants at two new doses between 1,2 and 2,3 and if the reduction in variability is deemed substantive, the 8 additional participants will be added.

The decision to proceed to the next dose cohort will be made jointly between the Sponsor and the Investigator, following a review of all available data.

In Cohort 5, statistical analyses will be descriptive, no formal statistical hypothesis testing will be applied.

### 12.4.3 Handling of missing values/censoring/discontinuations

No imputation of missing value will be considered for the primary analysis.

### 12.4.4 Sensitivity and Supportive analyses

#### Sensitivity analyses

Cohorts 1-4: It will be assessed through residual plots whether the model of the primary analysis gives a credible description of data. Other models with transformed response, non-constant error variance, and baseline covariates included may be attempted in order to see if the dose-response fit and conclusions hold up.

If substantial dropouts are seen prior to study day 4 (so that the primary end point is missing), the dose -response relationship will be reassessed under a model for informative drop out. This will be done in order to ensure that potential non-responders are not more likely to drop out.

## 12.5 Analysis of secondary endpoints

### 12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Not applicable.

### 12.5.2 Safety endpoints

The safety and tolerability will be evaluated by the following standard safety assessments; relevant findings from physical and neurological examinations, vital signs, hematology, chemistry, urinalysis, ECG evaluation, AE and SAE recordings. AEs potentially related to ECM accumulation (Section 10.2.4) or vasculitis (Section 10.2.3) will be summarized. The evaluations will be mostly descriptive; should a dose-dependent incidence in AEs be present, it will be quantified by Cochran-Armitage test for trend.

### 12.5.3 Pharmacokinetics

Cohorts 1-4: All participants who have evaluable PK data will be included in the PK data analysis. BLZ945 plasma pharmacokinetic parameters listed in Table 8-10 will be determined when feasible.

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Summary statistics of BLZ945 pharmacokinetic parameters will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented. A geometric mean will not be reported if the dataset includes zero values. Descriptive graphical plots of individual plasma concentration versus time profiles and mean concentration versus time profiles will be generated.

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Other plasma or urine PK parameters will be determined as appropriate.

Cohort 5: All participants who have evaluable PK data will be included in the PK analysis.

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The following BLZ945, Commercially Confidential Information plasma pharmacokinetic parameters will be estimated when feasible: Cmax, Tmax, AUClast, Tlast. Pharmacokinetic parameters will be listed by treatment and participant.

Summary statistics of BLZ945, Commercially Confidential Information pharmacokinetic parameters will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented. A geometric mean will not be reported if the dataset includes zero values. With only 4 samples and only up to 4 hrs post dose, it may not be possible to derive the PK parameters above.

Cohorts 1-5: the relationship between CYP2C8 polymorphisms and BLZ945 PK parameters will be assessed graphically and descriptively.

## 12.6 Analysis of exploratory endpoints

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Commercially Confidential Information

Commercially Confidential Information

## 12.7 Interim analyses

Commercially Confidential Information

## 12.8 Sample size calculation

### 12.8.1 Primary endpoint(s)

#### 12.8.1.1 Cohorts 1-4

It is assumed that up to 20 participants will provide a microglia fraction readout after 4 doses of study drug.

The operational characteristics of the design can be approximated by calculating the expected value of the Information matrix under various assumptions in the Hill constant and ED-50. As a guideline, it can be shown that when 20 participants are equally dosed with 300 mg, 450 mg, 600 mg, 900 mg and 1200 mg, and if a pure error variability in the model of 10% is assumed, then the expected coefficient of variation of the estimated ED-50 value is as displayed in Table 12-1. So, unless the ED-50 is below the range of concentrations tested then it will be estimated with a CV not exceeding 12%. The spacing between the concentrations considered is least 33% (from 900 to 1200 mg), so a precision of 12% must be considered good for anchoring the estimated ED-50 to one of the concentrations in the range. If at the extreme, the SD of the microglia reduction measurements is assumed to be the double, 20%, then the CV of the estimate will still be below 20% in most cases.

**Table 12-1 Percent CV estimate for ED-50 parameter**

| Hill constant/ED50 | 200 mg | 400 mg | 600 mg | 800 mg |
|---|---|---|---|---|
| 1 | 26.8 | 12.1 | 9.5 | 10.5 |
| 2 | 20.6 | 6.4 | 5.4 | 5.7 |
| 3 | 23.6 | 4.6 | 4.2 | 4.3 |

### 12.8.1.2 Cohort 5

Cohort 5 Commercially Confidential Information PET sub-study will recruit approximately 8 participants.

Sample size operating characteristics evaluations are based on a minimum of 24 participants (12 participants per treatment arm) contributing to the ECM accumulation assessments (esophagus wall thickness, LVEF, cardiac valve thickness and function and AEs of ECM accumulation); additional evaluations based on 30 participants (15 participants per treatment arm) are also provided. For the PET assessments, operating characteristics are evaluated using a maximum of 8 patients (4 participants per treatment arm).

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#### Percent change from baseline to Week 12 in Vt measured via PET scan

Based on the extensive burden to participants with ALS, the sample size for PET sub-study has been set to n=4 per treatment arm. The operating characteristics of the proposed sample size were assessed based on the probabilities to 1) observe a decrease of at least 20% in the point estimate of percent change from baseline to Week 12 in Vt, 2) observe a decrease between 10% and 20% in the point estimate of percent change from baseline to Week 12 in Vt, and 3) observe a decrease of less than 10% in the point estimate of percent change from baseline to Week 12 in Vt (Table 12-2). A reduction between 10% and 20% is expected to represent a clinically relevant change. For example, with a sample size of n=4 per treatment arm, if the true mean for percent change from baseline to Week 12 in Vt was a 21% reduction and the standard deviation (SD) was 17%, the probability to observe a decrease of 10% or higher in the point estimate is 90%. Across the scenarios considered, the probability to observe a reduction of 10% or higher in the point estimate is more than 80%, which is considered acceptable. A smaller sample size of n=3 was also evaluated in case of missing data due to treatment discontinuations. The assumptions on standard deviation and true mean reduction in Table 12-2 were made based on Cohort 2 (600 mg) results for percent change in Vt of precentral gyrus (Novartis data on file).

**Table 12-2 Probability to observe different outcomes for microglia Vt percent change from baseline to Week 12 assuming a true mean reduction of 21 percent**

| n | Assumed standard deviation (SD) | Prob (decrease at least 20% in point estimate) | Prob (decrease between 10% and 20% in point estimate) | Prob (decrease less than 10% in point estimate) |
|---|---|---|---|---|
| 3 | 17 | 54% | 33% | 13% |
| 3 | 21 | 53% | 29% | 18% |
| 4 | 17 | 55% | 35% | 10% |
| 4 | 21 | 54% | 31% | 15% |

### Changes from baseline to Week 12 in esophagus wall thickness (mm) and LVEF (%)

The operating characteristics of the sample size (using n= 12 and n=15 per treatment arm) for the esophagus wall thickness change from baseline to Week 12 (continuous variable measured in mm based on the esophagus CT scan) and for LVEF change from baseline to Week 12 (continuous variable measured for each patient in % based on the echocardiogram) were assessed via a precision approach within treatment arm (Table 12-3). Across the scenarios considered, the half width of the 95% CI for the esophagus wall thickness change from baseline to Week 12 is less than 1 mm, which is sufficient to assess clinically relevant changes. Similarly, the half width of the 95% CI for LVEF change from baseline to Week 12 is less than 1.3%, which is also considered sufficient. The assumption of a standard deviation (SD) of 0.89 for esophagus wall thickness change from baseline to Week 12 was derived based on an assumed SD of 2 mm from for the absolute measurement at both baseline and Week 12 (Berkovich et al 2000) and an assumed correlation value of 0.9 between baseline and Week 12. The assumption on the standard deviation for LVEF change from baseline to Week 12 was based on a SD of 4.9% fromKou et al 2014 for the absolute measurement at both baseline and Week 12 and an assumed correlation value of 0.9 between baseline and Week 12.

**Table 12-3 Precision of estimation for esophagus wall thickness change from baseline to Week 12 and LVEF change from baseline to Week 12**

| Variable | Assumed SD | n | Half-width of 95% CI |
|---|---|---|---|
| Esophagus wall thickness (mm) - change from baseline | 0.89 | 12<br>15 | 0.51<br>0.45 |
| LVEF (%) - change from baseline | 2.19 | 12<br>15 | 1.24<br>1.11 |

### Any worsening from baseline to Week 12 in cardiac valve thickness and cardiac valve function (stenosis and regurgitation)

The operating characteristics of the sample size (using n=12 and n=15 per treatment arm) for cardiac valve function, i.e. stenosis and regurgitation and for cardiac valve thickness (variables capturing any degree of worsening from baseline to Week 12) were assessed via a precision approach within treatment arm as measured by the half width of the 95% CI using Wilson's method (Table 12-4). For example, with n=12 per treatment arm, if the true event rate was 0.1, the half-width of the 95% CI is 0.18, which is considered acceptable.

**Table 12-4 Precision of estimation for cardiac valve thickness and cardiac valve function (stenosis and regurgitation) – any worsening from baseline to Week 12**

| Assumed true event rate | n | Half-width of 95% CI |
|---|---|---|
| 0.05 | 12 | 0.15 |
| 0.1 | 12 | 0.18 |
| 0.2 | 12 | 0.21 |
| 0.3 | 12 | 0.23 |
| 0.4 | 12 | 0.24 |
| 0.5 | 12 | 0.25 |
| 0.05 | 15 | 0.13 |
| 0.1 | 15 | 0.16 |
| 0.2 | 15 | 0.19 |
| 0.3 | 15 | 0.21 |
| 0.4 | 15 | 0.22 |
| 0.5 | 15 | 0.23 |

### Adverse events of ECM accumulation during the first 12 weeks of treatment

The operating characteristics of the sample size (using n=12 and n=15 per treatment arm) for AEs of ECM accumulation during the first 12 weeks of treatment were assessed based on the probability to observe at least 1 participant with AEs of ECAnd aM accumulation (Table 12-5). For example, with n=12 per treatment arm, if the true event rate was 10%, the probability of observing at least one patient with an AE of ECM accumulation is 72%, which is considered sufficient. The same calculations hold also for the probability to observe at least 1 participant with an event of any worsening in the cardiac thickness or in the cardiac valve function.

**Table 12-5 Probability of observing at least 1 participant with AEs of ECM accumulation during the first 12 weeks of treatment**

| Assumed true event rate | n | Probability |
|---|---|---|
| 0.03 | 12 | 31% |
| 0.05 | 12 | 46% |
| 0.10 | 12 | 72% |
| 0.2 | 12 | 93% |
| 0.5 | 12 | 100% |
| 0.03 | 15 | 37% |
| 0.05 | 15 | 54% |
| 0.10 | 15 | 79% |
| 0.2 | 15 | 96% |
| 0.5 | 15 | 100% |

# 13 Ethical considerations and administrative procedures

## 13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

## 13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g. advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

## 13.3 Data protection

Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to Novartis will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

## 13.4 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT / CTIS public website. In addition, after study completion and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical

trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT / CTIS public website etc.).

Summary results of primary and secondary endpoints will be disclosed based upon the global Last Participant Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings or site initiation visits.

Any data analysis carried out independently by the Investigator must be submitted to Novartis before publication or presentation.

## 13.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

# 14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

## 14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

# 15 References

References are available upon request

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# 16 Appendices

## 16.1 Appendix1: Liver safety monitoring

**Table 16-1 Liver event and laboratory trigger definitions**

| | Definition/ threshold |
|---|---|
| Liver laboratory triggers<br>If ALT, AST, TBL normal at baseline: | • ALT or AST > 5 × ULN<br>• ALP > 2 × ULN (in the absence of known bone pathology)<br>• TBL > 3 × ULN (in the absence of known Gilbert syndrome)<br>• ALT or AST > 3 × ULN and INR > 1.5 (in the absence of anticoagulation)<br>• Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)<br>• Any clinical event of jaundice (or equivalent term)<br>• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia<br>• Any adverse event potentially indicative of a liver toxicity* |
| If ALT or AST abnormal at baseline: | • ALT or AST > 3 x baseline |

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBL: total bilirubin; ULN: upper limit of normal.

*These events cover the following: Hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms.

Once a participant is exposed to study treatment, every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below.

Additional details on actions required in case of liver events are outlined in Table 16-2.

Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and GGT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 9.1.1 Discontinuation of study treatment), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event

- Thorough follow-up of the liver event should include
  - These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets, exclusion of underlying liver disease (as specified in Table 16-3).
  - Imaging such as abdominal US, CT or MRI, as appropriate

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

Refer to the SOM for additional details.

**Table 16-2 Follow up requirements for liver events and laboratory triggers**

| ALT or AST | Total Bilirubin (TBL) | Liver Symptoms | Action taken |
|---|---|---|---|
| **ALT or AST increase without bilirubin increase:** | | | |
| **If normal at baseline:**<br>ALT or AST >1.0-<3.0 x ULN | Normal<br>For participants with Gilbert's syndrome: No change in baseline TBL | None | • **No change to study treatment.**<br>• Monitor as considered appropriate by the investigator until recovery to previous baseline. |
| **If elevated at baseline:**<br>ALT or AST > 1.0 - <2.0 x baseline | | | |
| **If normal at baseline:**<br>ALT or AST > 3.0 x ULN | Normal<br>For participants with Gilbert's syndrome: No change in baseline TBL | None | • **No change to study treatment.**<br>• Measure ALT, AST, ALP, GGT, TBIL, INR, and albumin in 48-72 hours.<br>• Monitor closely until recovery to < 3.0 ULN or baseline.<br>• Follow-up for symptoms. |
| **If elevated at baseline:**<br>ALT or AST > 2.0 x baseline | | | |
| **If normal at baseline:**<br>ALT or AST > 5.0 x ULN | Normal<br>For participants with Gilbert's syndrome: No change in baseline TBL | None | • Interrupt study drug<br>• Measure ALT, AST, ALP, GGT, TBIL, INR, and albumin, in 48-72 hours.<br>• Obtain PK samples to determine exposure to BLZ945 and SoC.<br>• Collect an unscheduled blood sample for measurement of miR122.<br>• Follow-up for symptoms.<br>• Initiate close monitoring and |
| **If elevated at baseline:**<br>ALT or AST 3.0 x baseline AND 5 x ULN | | | |

| ALT or AST | Total Bilirubin (TBL) | Liver Symptoms | Action taken |
|---|---|---|---|
| | | | workup for competing etiologies (see Table 16.3). Monitor closely (e.g., weekly, or as considered appropriate by the investigator) until recovery to < 3.0 ULN or baseline.<br>• Study drug can be restarted at a lower dose level if liver enzymes return to < 3.0 ULN or baseline. |
| ALT or AST > 20.0 x ULN | Normal<br>For participants with Gilbert's syndrome: No change in baseline TBL | None | • Discontinue BLZ945 treatment. Consider interrupting riluzole until resolution of the liver event (if applicable).<br>• Obtain PK samples to determine exposure to BLZ945 and SoC.<br>• Collect an unscheduled blood sample for measurement of miR122<br>• Monitor closely LFTs until resolution[1] (ALT, AST, total bilirubin, albumin, INR, ALP and GGT, frequency at investigator discretion). |
| **ALT or AST increase with bilirubin increase and/or symptoms:** | | | |
| **If normal at baseline:**<br>ALT or AST > 3 x ULN | TBL > 2 x ULN (or INR > 1.5)<br>For participants with Gilbert's syndrome: doubling of direct bilirubin | None | • Interrupt study drug<br>• Measure ALT, AST, ALP, GGT, TBIL, INR, and albumin in 48-72 hours. If TBIL is elevated > 1.5 x ULN, direct and indirect bilirubin should be measured.<br>• Collect an unscheduled blood sample for measurement of miR122.<br>• Follow-up for symptoms.<br>• Obtain PK samples to determine exposure to BLZ945 and SoC.<br>• Initiate close monitoring and workup for competing etiologies (see Table 16-3). Monitor closely (e.g., weekly or as considered appropriate by the investigator) until |
| **If elevated at baseline:**<br>ALT or AST > 2 x baseline AND 3 x ULN | | | |
| **If normal at baseline:**<br>ALT or AST > 3 x ULN | Normal or elevated | Severe fatigue, nausea, vomiting, right upper quadrant pain | |
| **If elevated at baseline:**<br>ALT or AST > 2 x baseline AND 3 x ULN | | | |

| ALT or AST | Total Bilirubin (TBL) | Liver Symptoms | Action taken |
|---|---|---|---|
| | | | recovery to < 3.0 ULN or baseline.<br>• Upon recovery, collect blood sample for additional liver injury assay.<br>• Study drug can be restarted only if liver enzymes return to baseline and if another etiology is identified. |
| **Total Bilirubin (isolated)** | | | |
| Normal or no change from baseline | >1.5 – 3.0 ULN | None | • Maintain study treatment.<br>• Repeat LFTs within 48-72 hours, including measurement of direct and indirect bilirubin.<br>• Monitor LFTs closely (e.g., weekly, or as considered appropriate by the investigator) until resolution to ≤ 1.5 ULN or to baseline (ALT, AST, TBIL, albumin, PT/INR, ALP and GGT).<br>• Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin). |
| Normal or no change from baseline | > 3 - 10 × ULN (in the absence of known Gilbert syndrome) | None | • Interrupt treatment.<br>• Repeat LFTs within 48-72 hours, including measurement of direct and indirect bilirubin.<br>• Monitor LFTs closely (e.g., weekly, or as considered appropriate by the investigator) until resolution to ≤ 1.5 ULN or to baseline (ALT, AST, total bilirubin, albumin, PT/INR, ALP and GGT). |

| ALT or AST | Total Bilirubin (TBL) | Liver Symptoms | Action taken |
|---|---|---|---|
| Normal or no change from baseline | > 10 x ULN | None | • Discontinue treatment immediately.<br>• Measure LFTs within 48-72 hours, including measurement of direct and indirect bilirubin.<br>• Continue to monitor LFTs closely until resolution[1] (ALT, AST, direct, indirect and total bilirubin, albumin, PT/INR, ALP and GGT, frequency at investigator discretion). |
| [1] Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death. | | | |

Based on the investigator's discretion, additional investigation(s) for contributing factors for the liver event can be performed. These investigations may include: serology tests, imaging and pathology assessments, consultation with a hepatologist; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets, exclusion of underlying liver disease (see Table 16-3).

**Table 16-3 Alternative causes of liver disease and related assessments**

| Disease | Assessment |
|---|---|
| Hepatitis A, B, C, E | • IgM anti-HAV; HBsAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA |
| CMV, HSV, EBV infection | • IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV |
| Autoimmune hepatitis | • ANA & ASMA titers, total IgM, IgG, IgE, IgA |
| Alcoholic hepatitis | • Ethanol history, GGT, MCV, CD-transferrin |
| Nonalcoholic steatohepatitis | • Ultrasound or MRI |
| Hypoxic/ischemic hepatopathy | • Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion<br>• Ultrasound or MRI |
| Biliary tract disease | • Ultrasound or MRI, ERCP as appropriate. |
| Wilson disease | • Caeruloplasmin |
| Hemochromatosis | • Ferritin, transferrin |
| Alpha-1-antitrypsin deficiency | • Alpha-1-antitrypsin |

## 16.2 Appendix 2: Specific Renal Alert Criteria and Actions and Event Follow-up

**Table 16-4 Specific Renal Alert Criteria and Actions**

| Renal Event | Actions |
|---|---|
| Confirmed serum creatinine increase 25 – 49% | • Consider causes and possible interventions<br>• Follow up within 2-5 days |
| Serum creatinine increase ≥ 50 % | |
| **OR if <18 years old, eGFR ≤ 35 mL/min/1.73 m$^2$**<br>New onset dipstick proteinuria ≥ 3+ OR<br>Protein-creatinine **ratio** (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory) | • Consider causes and possible interventions<br>• Repeat assessment within 24-48h if possible<br>• Consider drug interruption or discontinuation unless other causes are diagnosed and corrected<br>• Consider participant hospitalization and specialized treatment<br>• Consider causes and possible interventions<br>• Assess serum albumin & serum total protein<br>• Repeat assessment to confirm<br>• Consider drug interruption or discontinuation unless other causes are diagnosed and corrected |
| New onset hematuria ≥ 3+ on urine dipstick | Assess & document<br>• Repeat assessment to confirm<br>• Distinguish hemoglobinuria from hematuria<br>• Urine sediment microscopy<br>• Assess sCr<br>• Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation<br>• Consider bleeding disorder |

[+] Corresponds to KDIGO criteria for Acute Kidney Injury

Additional specialized assessments are available to assess renal function or renal pathology. *(Note: In exceptional cases, when a nephrologist considers a renal biopsy, it is recommended to make slide specimen available for evaluation by the RSG to potentially identify project-wide patterns of nephrotoxicity.)*

Whenever a renal event is identified, a detailed participant history and examination are indicated to identify and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5-minute rest, with an appropriate cuff size)
- Signs and symptoms like fever, headache, shortness of breath, back or abdominal pain, dysuria or hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other diseases or causes, e.g., dehydration due to delirium, tumor lysis

**Table 16-5 Renal Event Follow Up**

| |
|---|
| Assess, document and record in CRF<br>• Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells<br>• Blood pressure and body weight<br>• Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid<br>• Urine output |
| Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF |
| Monitor participant regularly (frequency at investigator's discretion) until -<br>• Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr, or ACR <300 mg/g Cr) or<br>• Event stabilization: sCr level with ±10% variability over last 6 months or protein- creatinine ratio stabilization at a new level with ±50% variability over last 6 months.<br>• Analysis of urine markers in samples collected over the course of the DIN event |

## 16.3 Appendix 3: Guidance for the identification of potential cases of vasculitis and their follow-up

### 16.3.1 Identification of potential cases of vasculitis

The identification of potential cases of vasculitis should be based on the occurrence of signs and symptoms based on a detailed medical history and physical examination, along with supportive laboratory evidence.

A list of clinical manifestations of vasculitis is provided in Table 16-6.

**Table 16-6 Clinical manifestations of vasculitis**

| System organ involved | Clinical manifestations |
|---|---|
| General | Myalgia, arthralgia / arthritis, fever, weight loss |
| Cutaneous | Infarct, purpura, ulcer, necrosis, rash |
| Mucous membranes / eyes | Mouth ulcers, genital ulcers, adnexal inflammation, significant proptosis, red-eye conjunctivitis / blepharitis / keratitis*, red-eye epi/scleritis*, blurred vision*, uveitis*, retinal involvement* |
| Ear Nose Throat | Bloody nasal discharge, nasal obstruction, nasal crusting, sinus involvement, hearing loss*, hoarseness / stridor (due to subglottic stenosis#) |
| Chest | Persistent cough, dyspnoea or wheeze, hemoptysis / hemorrhage, nodules or cavities#, pleural effusion#, infiltrate# |
| Cardiovascular | Valvular heart disease#, pericarditis, ischemic cardiac pain#, cardiomyopathy#, congestive cardiac failure |
| Gastrointestinal | Bloody diarrhoea, severe abdominal pain due to ischemia# or peritonitis |
| Renal | Hypertension, proteinuria, hematuria, red cell casts in urine, deterioration of renal function |
| Nervous system | Sensory peripheral neuropathy, motor mononeuritis multiplex |

* Additional specialist consultation may be required for further evaluation and management;
# Use of imaging techniques required for the evaluation of these clinical manifestations

Patients will be instructed to contact the investigator immediately in the event that they experience any sign or symptom of vasculitis. If investigators suspect a case of vasculitis, it is recommended that BLZ945 administration is temporarily interrupted until further investigations confirm or refute the case.

A detailed history of signs and symptoms, including time to onset, severity and evolution of symptomatology should be documented in the patient's charts as well as history of exposure to new medications (if applicable). Changes in severity of symptoms as well as resolution of symptoms upon drug discontinuation should also be recorded. If any lesions are noticed by the patient (e.g., skin or mucous membranes), photographs may be taken and showed to the investigator and/or specialist to facilitate clinical assessment.

### Physical examination

Vital signs will be collected at all site visits and during home nursing visits in accordance with the assessment schedule described in Table 8-5.

A physical examination will be performed by the investigator or qualified delegate at all site visits as scheduled per Table 8-5 or, if necessary, at unscheduled visits. The examination will include general appearance, head, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, skin (e.g., purpura), extremities, vascular and neurological (e.g., paresthesia and dysesthesia) assessments.

### Laboratory assessments

Laboratory assessments will be performed at baseline and at the site and home nursing visits as scheduled per Table 8-5, or at unscheduled visits. These assessments will include complete blood count, liver function tests, renal parameters such as creatinine, BUN and urinalysis (macroscopic and microscopic panel), cardiac enzymes (CK-MB, troponins) and markers of inflammation (e.g., ESR and CRP). For a full list of laboratory assessments, please refer to Section 8.4.1.

In case of elevations in ESR and CRP above the thresholds defined below in Table 16-7, additional diagnostic work should be performed to look for signs of symptoms indicative of vasculitis (e.g., physical examination). Unscheduled laboratory assessments might also be performed in case of new onset of signs and symptoms, if required by the investigator.

**Table 16-7 Laboratory triggers for additional assessment**

| Parameter | Threshold |
|---|---|
| CRP | • CRP ≥ 20 mg/L in participants with baseline CRP < 10 mg/L<br>• Any increase of additional 10 mg/L in participants with baseline CRP ≥ 10 mg/L |
| ESR | • ESR ≥ 30 mm/hr in female participants with baseline ESR < 15 mm/hr<br>• Any increase of additional 15 mm/hr in female participants with baseline ESR ≥ 15 mm/hr<br>• ESR ≥ 20 mm/hr in male participants with baseline ESR < 10 mm/hr<br>• Any increase of additional 10 mm/hr in in male participants with baseline ESR ≥ 10 mm/hr |
| Expedited reporting in case of results above threshold | |

As constitutional symptoms such as fever, arthralgia, myalgia and weight loss, and laboratory features including elevations in ESR and CRP can be encountered in other conditions, it is important to exclude other diagnoses that might account for the presenting signs and symptoms (e.g., bacterial infections).

### 16.3.2 Clinical management of potential cases of vasculitis

For any potential case of vasculitis, the extent and location of vasculitis involvement should be assessed. For this purpose, the evaluations listed above may be supplemented by other investigations (e.g., urinalysis, serum creatinine and BUN in case of suspected renal involvement).

Tissue biopsy may be performed to confirm the diagnosis of vasculitis, with the choice of the site for biopsy determined by the pattern of organ involvement.

For cases of suspected vasculitis, anti-histone antibody levels should be measured, and assays for anti-neutrophil cytoplasm antibodies (ANCA) should be performed using both immunofluorescence and enzyme-linked immunosorbent assay (ELISA).

Depending on the site of involvement, additional follow-up of potential cases of vasculitis should include:

- Referral to a rheumatologist for a complete evaluation of the symptomatology and clinical course of vasculitis
- Additional referral to specialist consultation based on the anatomical location of tissue involvement is required, e.g.:
    - Assessment of skin lesions and rashes by a dermatologist; the evaluation of skin lesions should include a skin biopsy.
    - Referral to a nephrologist for further evaluation in the event of suspected renal involvement (e.g., renal biopsy as appropriate per local practice)
    - Additional specialist consultation may be considered in case of involvement of other anatomical sites (e.g., retinal involvement).